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ANNALS OF
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VOLUME 10 APRIL, 1937 NUMBER 10

THE THYREOACTIVATOR HORMONE; ITS ISOLATION FROM THE ANTERIOR LOBE OF THE BOVINE PITUITARY GLAND AND ITS EFFECTS ON THE THYROID GLAND *

By EDUARD UHLENHUTH, *Baltimore, Maryland*

THE results of the work to be summarized here and leading to the conclusion that the anterior pituitary manufactures and excretes a specific thyreoactivator hormone by means of which the hypophysis controls the activity of the thyroid, were reported first, by Uhlenhuth and Schwartzbach, in 1926, at the annual meeting of the American Zoölogists in Philadelphia.[3] A brief account covering all the essential points of evidence was published by Uhlenhuth and Schwartzbach, in 1927.

The history of investigations pertaining to the subject with which the present article is dealing, has been discussed briefly, yet in its most essential features, in "Endokrinologie, 1935, xv, 329–342"; in the latter article as well as in many other articles due credit has been given to those who preceded the author. It is for this reason and because of the limitations of space that the author had to omit all references to the work of other investigators.

As we were guided in our work on the thyreoactivator by previous comparative studies of the structure of the thyroid of amphibians (salamanders) and as these morphological studies had yielded important results concerning the functional significance of certain structures of the thyroid and concerning the biological evaluation of pathological conditions of the human thyroid, these comparative morphological studies will appropriately

* Van Meter Prize Essay, 1936. Read before the American Association for the Study of Goiter, June 9, 1936.

From the University of Maryland Medical School.

The work reported in this essay was conducted under the auspices of the Medical School of the University of Maryland, and with the collaboration of the author's students and associates. Financial aid was received from the "Julius Friedenwald Fund for Medical Research," from the "Weaver Fund" and from the "Hitchcock Fund," all three of the University of Maryland Medical School, from the "Elizabeth Thompson Science Fund" of Harvard University and from a gift received personally by the author through the generosity of Mr. Victor Bloede of Baltimore.

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form the introduction to our physiological experiments. In order to emphasize that, although we can submit ample evidence indicating a humoral control of thyroid activity, we nevertheless do not believe that the nervous system has no part in regulating thyroid activity, a report of our recent investigations bearing on the nervous control of the thyroid, is appended.

I. A Functional Interpretation of Thyroid Structure

At the time when we became interested in the study of the thyroid gland, a satisfactory functional interpretation of the thyroid structure was not available, in spite of the splendid work of anatomists, physiologists, and clinical scientists such as R. B. Bensley, David Marine, McCallum, Allen Graham, Louis Wilson and others. In fact there was no agreement as to the structural picture of a highly active, as contrasted to a relatively dormant, thyroid. There was even no general consent as to the significance of the thyroid colloid. Many reports appeared at that time maintaining that a scarcity of colloid indicates a low activity, while some English

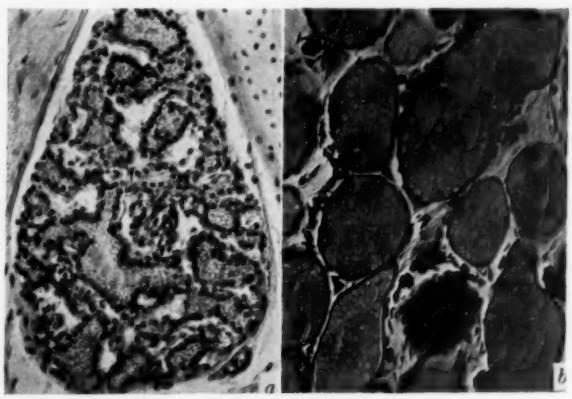

Fig. 1. Showing two different thyroid types of adult salamanders of two different species (same magnification). (*a*) Gland of adult marble salamander during spring activity, resembling exophthalmic goiter; note star-shaped follicles and numerous colloid vacuoles. (*b*) Gland of aquatic Colorado axolotl, resembling colloid goiter; note large roundish follicles and absence of colloid vacuoles. (From Roux's Arch., 1927, cix, 611; figures 27 and 34.)

surgeons (Williamson and Pearse) contended that the colloid is a waste product which, once deposited, never again leaves the lumen of the follicle.

It appeared to us that many of these important questions could be answered, by studies of the thyroid in a group of animals in which this gland normally presents a wide variety of functional states and structural types. Such a group of animals presented itself to us in the so-called salamanders or tailed amphibians. In these animals thyroids ranging from the structure of a human exophthalmic goiter gland to that of a human colloid goiter are found normally (figure 1). It was soon discovered, moreover, that closely allied species and even varieties of the same species possessed widely differing thyroids which not only represented a fixed and

inherited type characteristic for each variety, but were associated with a biology which could be traced back to the functional level of the particular thyroid type. In addition these animals had been previously found to react promptly, when in an aquatic stage, upon administration of thyroid with transformation (metamorphosis) into a terrestrial stage (Gudernatsch, 1913). In this peculiarity a simple means is afforded to use metamorphosis as a test for thyroid activity. Hence an extensive study of the thyroid of salamanders was undertaken. A detailed account of this work was published in 1927.[5] The essential results of this work are the following:

(*a*) *The Colloid Plays an Essential Rôle in the Specific Function of the Thyroid.* It was found that during developmental stages at which the thyroid does not function, colloid is stored in the follicles. At the beginning of a functional period it is suddenly, within 24 hours, released from the follicles, but is stored again when the functional period has passed. In a quantitative study of 40 thyroids the total mass of thyroid tissue, the mass of epithelium and the mass of colloid could be expressed in gram weight.* In the graph of figure 2 are shown the absolute weights of the colloid and of the epithelium. It is noticed that during the inactive period colloid is stored, while during the functional period 50 per cent of the stored colloid is released suddenly; several days later the follicles are refilled and the mass of colloid again increases. The same events are shown in figure 3 in which the amount of colloid is expressed in percentages of the total thyroid mass. Evidently colloid is released precisely at the time of thyroid activity. The release of the stored colloid is an essential feature of thyroid activity; the colloid is essential in the specific function of the thyroid gland.[1, 2]

(*b*) *Structural Characters of Active and Dormant Thyroid.* Selecting different developmental stages of the thyroid of the same species, and studying, furthermore, the thyroids of different species in which the degree of thyroid activity could be determined by its physiological effects on the biology of the species, we are able to recognize structural characters distinguishing the active from the dormant thyroid.[5] These are:

Active Thyroid	*Resting Thyroid*
(1) Stainable colloid absent or scarce.	Large quantities of stainable colloid.
(2) Walls of follicles collapsed, shape of follicles star-like (with papillae and solid cell columns).	Follicles roundish, with regular outlines.
(3) Colloid vacuoles numerous.	Colloid vacuoles scarce or absent.
(4) Cells enlarged and swollen.	Cells small and flat.
(5) Cells filled with secretion vacuoles (for which we introduced the term "Anderson Vacuoles").	Cytoplasm not vacuolized.

In figure 4 are shown the patterns of an active and of a dormant gland of the same species, elucidating points 1 and 2. The difference in the number of colloid vacuoles, existing between an active and an inactive gland is brought out well in figure 1. In figure 5 are illustrated the increase in

* For details of technic see "W. Roux's Arch. f. Entwicklgsmech., 1927, cix, 616."

Figure 2.

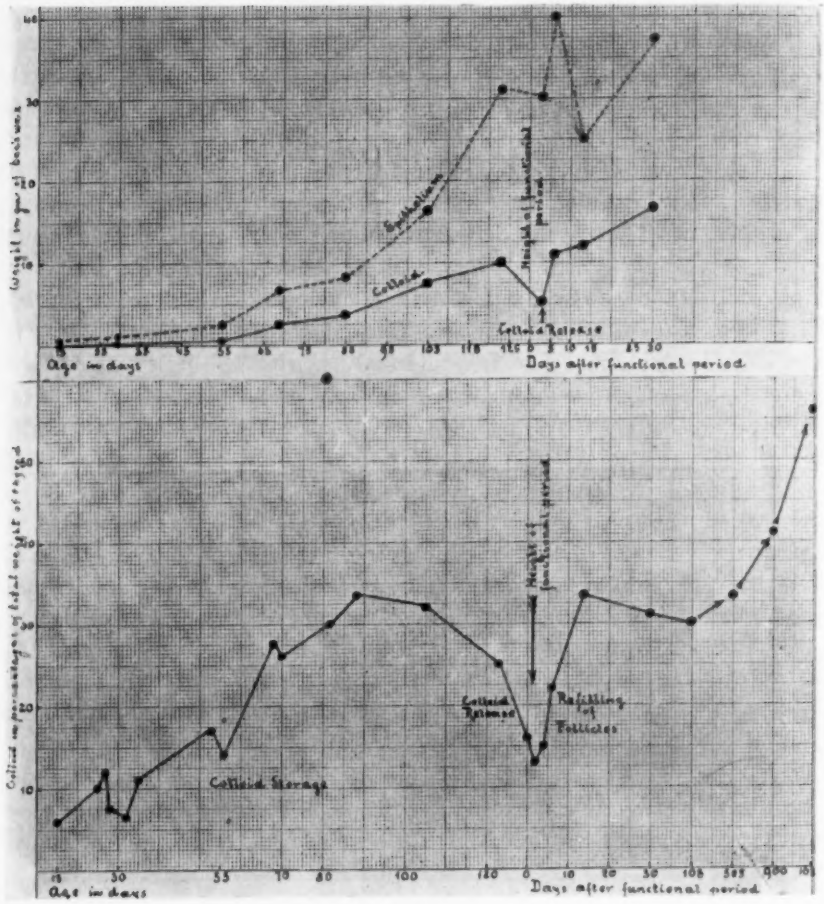

Figure 3.

FIG. 2. Showing a functional cycle of the thyroid, with increasing amounts of colloid during "Storage" phase, and colloid release (drop in the lower one of the two curves) during "Releasing" or active phase.

FIG. 3. Showing the functional cycle of the thyroid; colloid expressed in percentages of total thyroid weight, emphasizing the sharp drop in colloid amount during the "Releasing phase," relative to the other thyroid tissues. (See Roux's Arch., 1927, cix, 620, table 2.)

the cell size and the vacuolization of the cytoplasm so characteristic of the active thyroid.

(*c*) *The "Two-Phase Cycle" of Thyroid Activity.* In studying the periods of thyroid activity in one species and correlating them with the corresponding structural appearances it was found that thyroid activity is cyclic and that the entire cycle consists of two phases, a "storage phase" and a "releasing phase." During the former the cells manufacture actively the colloid, excreting it, however, only in one direction, into the lumen of

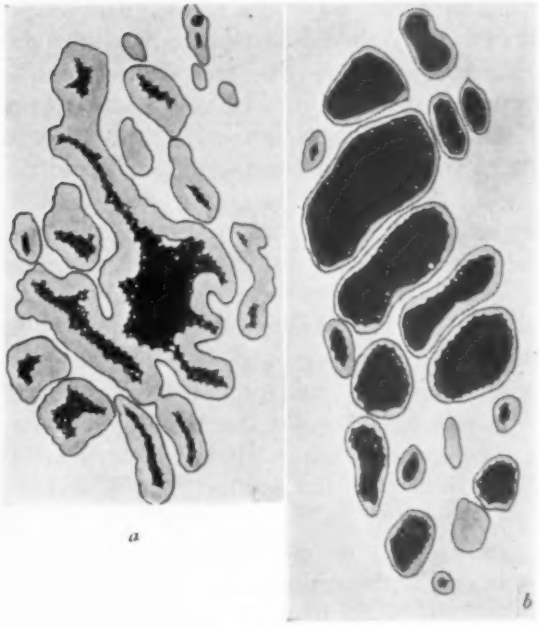

FIG. 4. Showing changes in thyroid pattern during functional cycle of thyroid of same species. (*a*) "Releasing phase," during height of spontaneous (physiological) activity. (*b*) "Storage phase" during dormant period. (Redrawn from Roux's Arch., 1927, cix, 611.)

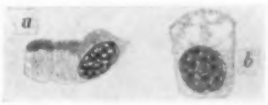

FIG. 5. Cells of (*a*) dormant (storage phase) and (*b*) active (releasing phase) thyroid, at same magnification. Note increased cell size and presence of intracellular secretion vacuoles in active gland. (Redrawn from figures 72 and 61 in Roux's Arch., 1927, cix, 611.)

the follicle where it is stored and eventually leads to a distention (figures 4*b* and 1*b*), or even bag-like enlargement of the follicles. During the latter phase the colloid is allowed to escape from the follicles into the blood stream; if the release takes place at a faster rate than the manufacture of colloid, the follicles collapse and assume a star-like shape, the lumina of the follicles changing into mere slits (figure 4*a*). As the physiological effects of the thyroid hormone are apparent only during the releasing phase of the cycle, the terms "active" or "activated" will be applied henceforth only to thyroids which are in the releasing phase.

(*d*) *Releasing Factor.* On the basis of differential reactions to iodine as observed by Swingle in frogs, and in salamanders in our own laboratory, and guided by the behavior of species in which the thyroid remains permanently in the storage phase, we were led to the conclusion that only the

storage phase is controlled by the thyroid's own, intrinsic powers, while the releasing phase is caused by the effects, upon the thyroid, of an extrinsic agent which we called at that time the " releasing factor " and the nature of which was unknown to us. Our evidence seemed to suggest that the manufacture of colloid and its excretion into the lumen of the follicles are primary and essential functions of the thyroid cells and going on continuously, their rate being dependent only on the degree of distention of the follicles; but that the unique peculiarity of the thyroid, its closed vesicles, has called forth the development of a special extrinsic mechanism controlling the release of the stored secretion from these vesicles.[5]

(*c*) *Interpretation of Human Thyroid Pathology.* A comparison of different types of salamander thyroids with human pathologic thyroids immediately revealed striking resemblances, especially between exophthalmic goiter and the " releasing type " on the one hand, and between colloid goiter and the " storage type " on the other hand. These resemblances were expressed in nine structural and three functional points for exophthalmic goiter, and in eight structural points for colloid goiter. Since it appeared that the two types are merely different stages of one functional cycle and the normal responses of the thyroid to corresponding stimuli, the conclusion seemed unavoidable that in man likewise these two thyroid types could not be considered as the result of a pathological thyroid, but would, on the contrary, indicate the presence of a normal thyroid in the possession of all its normal potentialities and capable of responding normally to the presence or absence of the extrinsic releasing factor. It was suggested that in the case of exophthalmic goiter the disturbance might have to be looked for in the extrinsic releasing factor which in this case appeared to be working overtime.[5, p. 732]

The evidence in our hands concerning the existence of an extrinsic releasing factor was so convincing that a vigorous search was begun immediately. These studies which were conducted in collaboration with S. S. Schwartzbach, led finally (summer, 1926) and after three years of entirely unsuccessful work with nerve stimulating drugs, to the discovery of the thyreoactivator.

II. Humoral Excitation of the Thyroid Gland

Up to 1926 no agent was known by which an artificial stimulation of the thyroid gland could be effected. Our task, as we saw it then, was that of finding a substance by means of which the thyroid could be forced experimentally from the storage phase into the releasing phase, producing thus a thyroid type which would exhibit the essential structural features of this gland at the height of its releasing activity and would therefore resemble the thyroid of a metamorphosing salamander or the human exophthalmic goiter gland.

The results of this work may be summarized under the following points:

(*a*) *The Extraction of the Thyreoactivator* (*TA*). In our first experiments conducted together with Schwartzbach,[3, 4, 7, 8, 9, 10] three different kinds of bovine pituitary anterior lobe (AL) powder were used: Armour's commercial desiccated AL; and AL powder prepared according to our prescriptions, especially for us by Armour & Co.*; and a powder prepared by ourselves. At present all powders are prepared in our own laboratory by the following method.

The anterior lobes are separated from the posterior lobes by ourselves in the abattoirs,† not later than 40 minutes after the death of the animals. So far only steer pituitaries have been used. Immediately after arrival in the laboratory the glands are cut into small pieces, spread on glass plates and air-dried overnight, by electric fans. If properly manipulated, the glands, neither after this procedure nor at any time later, exhibit any odor of putrefaction. The air-dried material is then desiccated for six days over calcium chloride, ground through a 40 mesh sieve, placed in glass-stoppered bottles and kept, over calcium chloride, in a refrigerator. This powder retains its effectiveness for at least six months.

The powders were extracted, in our first experiments, in acidified Ringer solution (0.5 c.c. of glacial acetic acid per 100 c.c. Ringer) and only occasionally in plain Ringer, the extraction being performed by heating the mixture just to the boiling point. At present plain Ringer is used and the extraction is carried out as follows: A quantity of powder is added to the Ringer solution in such proportions that the final extract will contain TA equivalent to 25 to 200 mg. of dried powder per 0.5 c.c. fluid. The mixture is carefully heated until it almost boils, is filtered immediately, taken up into a syringe and injected as soon as possible.

The appearance of such an extract is that of a clear and markedly pinkish fluid. If the mixture is watched during the process of heating, it is observed that when a temperature close to the boiling point is reached, a loose and flocculent precipitate appears, mingling with the powder particles. On standing, the entire mass rises while previous to the formation of this precipitate the AL particles sink to the bottom.

In more recent experiments to be published elsewhere, extracts were prepared by permitting the mixture to stand overnight in a refrigerator and filtering it without heating. Filtration in this instance proceeds very slowly as the fluid is of thick, syrupy consistency. If, after filtration, this fluid is heated, the same loose precipitate observed with the previous technic will form. Extracts prepared by the technic of cold extraction contain thyreoactivator, but we do not know as yet what yield can be obtained by this method. We suspect that it does not result in a separation of the TA from the other hormones contained in the AL.

When extracts prepared by heating are cooled on ice or are permitted to stand for several hours, a fine precipitate falls. Although we have not made specific tests we are under the impression that cooling or standing decreases the strength of the extract.

When the powder is extracted in acidified Ringer, neutralization by N/10 NaOH is necessary. If this is carried beyond a certain point, a precipitate begins to form. Edgar Van Slyke found that the precipitate appears at a pH of 6.8. In experiments conducted together with Norman Wilson we found that extracts precipitated with NaOH and filtered free of the precipitate, have practically lost their power of meta-

* The author takes great pleasure in acknowledging here the valuable assistance and coöperation rendered in this phase of the work by Dr. Frederick Fenger of Armour and Co.

† The author, in behalf of his students and the University of Maryland, wishes to express his gratitude to Mr. Robert Fox, of Greenwald and Company, Baltimore, for the fine spirit of coöperation and generosity which he and his firm have shown to us throughout our work and which in no small measure have made possible our success.

morphosing the larval salamanders, suggesting that the precipitate carries down the TA.

Although we have not attempted chemical purification of the extracts, we succeeded, nevertheless, by the simple technic of heating the extracts, in isolating the TA from most of the other AL hormones. The gonads of hundreds of animals were examined; never have we observed gonadotropic effects of our extracts. Together with Frank H. J. Figge [20] we have shown that the hypophysis of the animal to be injected may be removed without decreasing, in any degree, the response to the thyroid-stimulating property of the extracts. We are not informed as to a possible adrenotropic component in our extract as the amphibians are not suitable material for such a test. The extract contains, however, some materials which produce, independently of the activity of the thyroid gland, both exophthalmos and a certain degree of tissue dehydration, as observed by Figge and Uhlenhuth [20] in thyroidectomized animals injected with the extract.

(*b*) *Effects of TA on Thyroid Structure:* as shown by S. S. Schwartzbach, Guy P. Thompson, and Karl Mech (see references 3; 4; 6, p. 595; 9 and 26).

(1) TA, when injected intraperitoneally, reproduces exactly the structure which had been previously found characteristic of the active (releasing) thyroid.

(2) The colloid is released (see below), the follicles collapse and the lumina become slit-like.[6, 26]

(3) The cells are enormously increased in height and in size generally.

(4) Intracellular secretion vacuoles are present and may replace almost completely the cytoplasma (see references 6, fig. 95; *22*; *26*).

(5) Colloid vacuoles appear in large numbers.

(6) In addition, more recently it was found that the Golgi apparatus increases greatly in mass at first and later on breaks up into small particles.[17, 22]

(*7*) And further, that after prolonged injections the unstainable intracellular vacuoles are replaced more and more by deeply staining secretion droplets.[22]

In figure 6 are shown the more general changes of the thyroid structure as they appear in histological sections. Comparing a normal control (figure 6*a*) with the thyroid after six TA injections (figure 6*b*), the swelling and liquefaction of the cells are apparent. After 14 TA injections the almost complete absence of colloid may be seen (figure 6*c*); and after *22* injections (figure 6*d*) the presence of numerous droplets in the cells is evident.

In figure *7* is illustrated the vacuolization and liquefaction of the cells as seen in the fresh thyroid of TA injected animals. By the technic of examining the fresh thyroid of the salamander in the moist chamber and with oil immersion, only two days are required to determine whether or not the extract is effective.

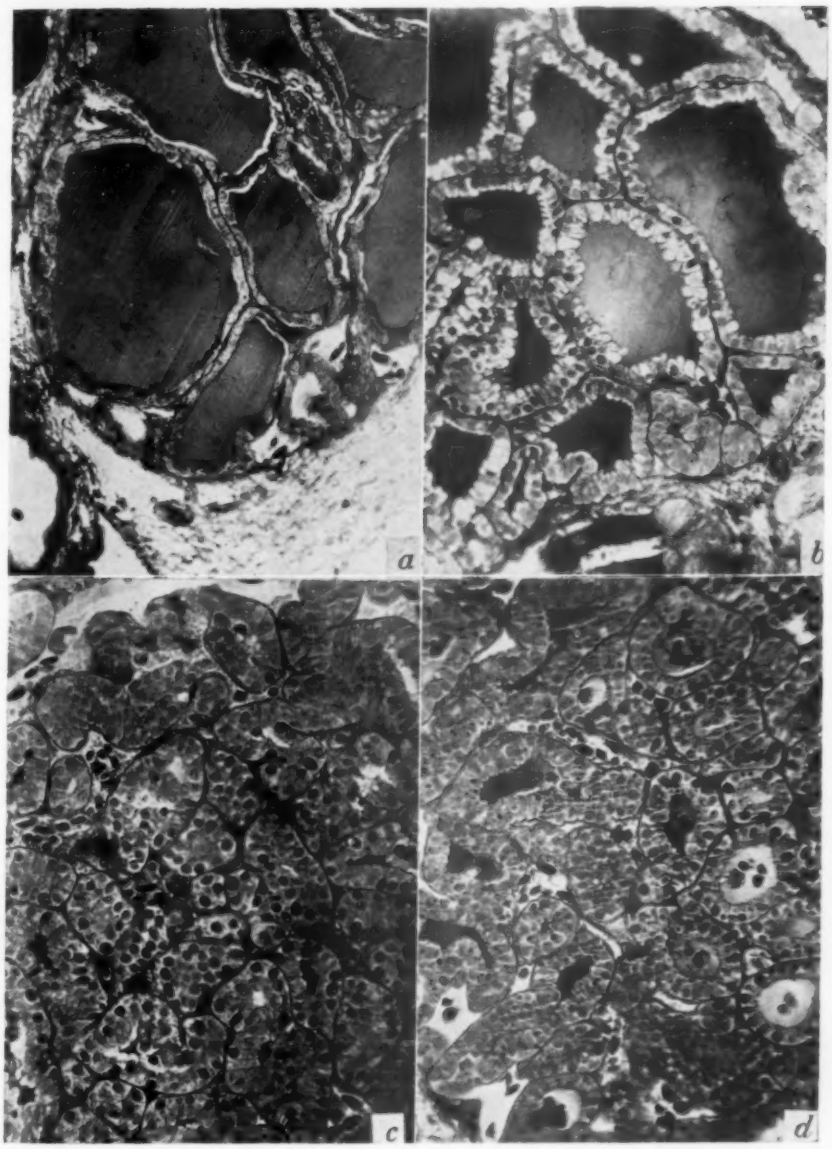

FIG. 6. Gross histological appearance of thyroid activated by TA. (*a*) Normal control. Follicles large, epithelium flat, cytoplasma without secretion vacuoles. (*b*) After 6 TA injections. Follicles beginning to collapse, cells greatly enlarged, cytoplasma largely replaced by intracellular secretion vacuoles. (*c*) After 14 TA injections; nearly complete release of colloid. (*d*) After 22 TA injections; cells filled with deeply stained "Colloid droplet."

In figure 8 are shown the cytological changes taking place in the thyroid cells of adult animals after continued TA injections, as seen in microscopical sections. In figure 8*a* are illustrated the cells of a normal, resting thyroid; the cells are filled with very small granules each of them contained within

a vacuole. These granules can be seen in the fresh thyroid and can be stained vitally, in the living animal, with neutral red; for this reason we called them NR-granules. In the fresh gland they move slowly about within

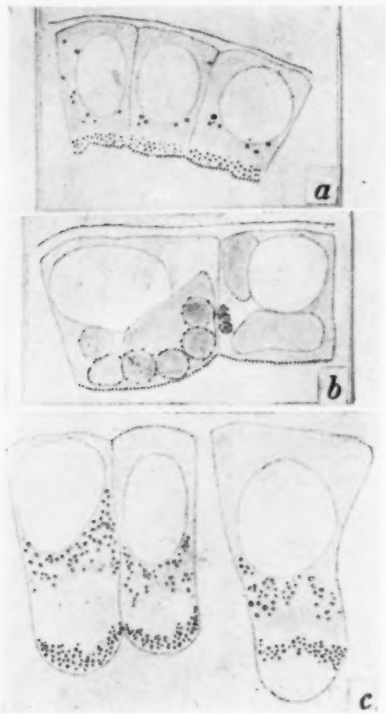

FIG. 7. Cells of larval thyroid activated by TA injections as seen in the fresh gland under high magnifications. (*a*) Normal control; neutral red granules numerous, but no secretion vacuoles. (*b*) Activated gland; neutral red granules absent, but many large secretion vacuoles present. (*c*) Activated gland; entire apical region vacuolized. (From Uhlenhuth, Schwartzbach and Thompson, Endokrinologie, 1935, xvi, 9–19, figure 1.)

the vacuole, a movement different from Brownian movement. In addition to the NR-granules, few small deeply staining droplets are present, likewise contained within vacuoles; in most of the dormant glands, however, droplets are absent.

In successful microscopical sections the NR-granules and the vacuoles containing them are of such excellent definition that they show perfectly well in photographs. In figure 9 is shown a follicle from a normal gland; it will be noticed that nearly the entire cell body consists of nothing but these small vacuoles containing each one granule. Owing to this peculiarity the protoplasm appears honeycombed or foamlike, a structure claimed long ago by Bütschli as characteristic for all protoplasm.

Figure 8*b* shows the thyroid after six TA-injections; the cells have now greatly increased in size and the cell plasma is almost completely replaced

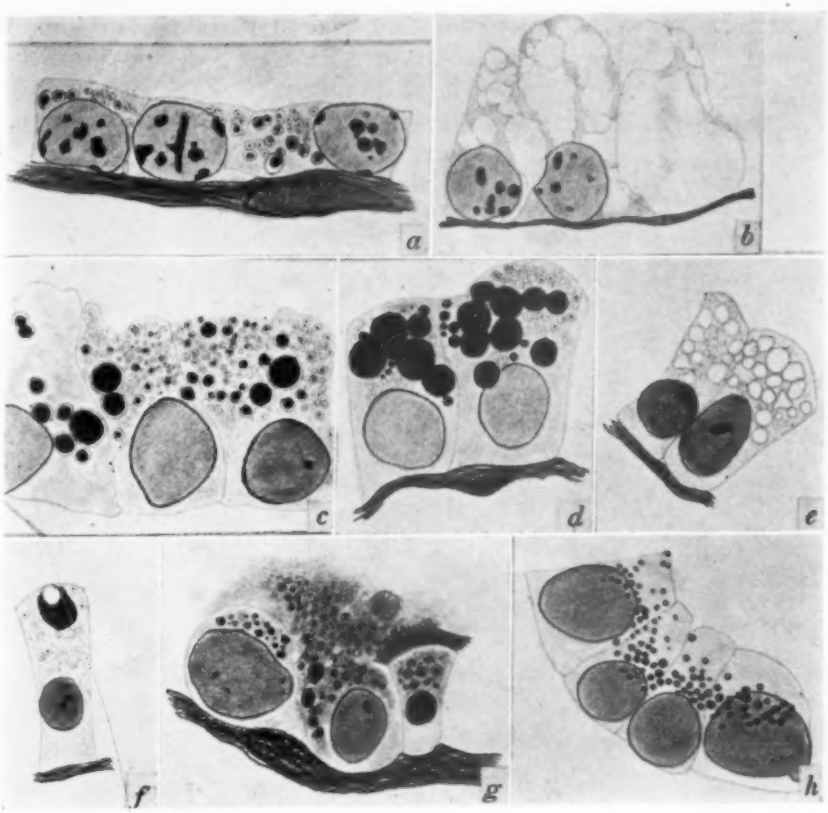

FIG. 8. Cytology of adult thyroid activated by TA, as seen in histological sections. (*a*) Normal gland; (*b-h*) different phases of functional activity of thyroid cells.

by large lacunae-like vacuoles. It will be noticed that the NR-granules have disappeared. In figure 8*c* is seen a thyroid after 15 TA-injections. The vacuoles have disappeared, while the NR-granules have reappeared. At the same time deeply stained colloid droplets have developed. These are of variable size and as they are contained each in a vacuole, the small droplets cannot be distinguished from the large NR-granules. As the number of injections increases, the number and size of intracellular droplets increase (figure 8*d*). Frequently cells are found now in which the droplets have dissolved into an unstainable fluid deposited in vacuoles (figure 8*e*). Under physiological conditions the colloid is excreted, by the cells, not in corpuscular form, but as a liquid, by a process of diffusion through the cell walls. Upon excessive stimulation, however, such as is effected by large numbers of TA-injections, colloid passes from the cells into the follicle lumen in corpuscular form; either droplets (figure 8*f*, partly liquefied droplet) are excreted or the whole apex (figure 8*g*), or even whole cells are shed. Especially this latter process results in degeneration and disintegration of large

numbers of cells. If TA-injections are discontinued the thyroid, after some time, returns to its normal condition. An arrangement of the granular content of the cell shown in figure 8*h*, with the granules occupying a position close to the nucleus, is a very characteristic stage of this reconstruction period.

FIG. 9. Photograph of normal thyroid cells to show vacuoles containing "Neutral red granules."

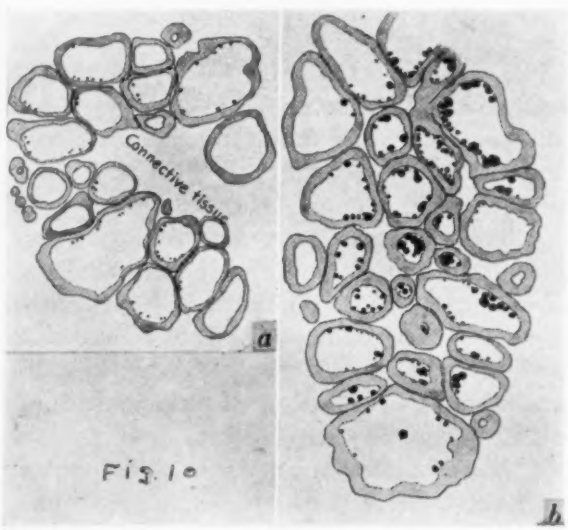

FIG. 10. Showing the increase in size and number of colloid vacuoles (black dots) in the thyroid activated by TA (*b*) as compared to normal thyroid (*a*). (Taken from Figge and Uhlenhuth, Physiological Zoölogy, 1933, vi, 450–465, Plate I, figure *d*7.)

The colloid vacuoles as seen after certain fixatives (Zenker) are illustrated in figure 10; in the gland activated by TA they are greatly increased in numbers as well as in size. The changes in the Golgi apparatus, effected by TA-injections will be evident from an inspection of figure 11.

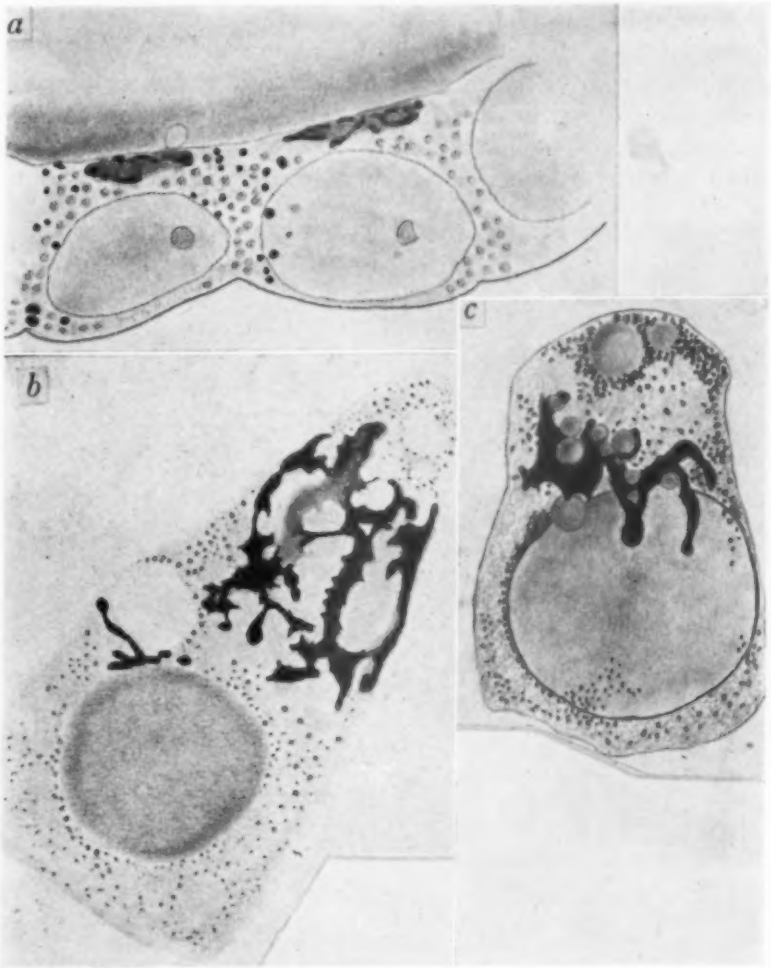

FIG. 11. Showing the increase in size of Golgi apparatus in the cells of thyroid activated by TA (*b* and *c*) as compared to dormant thyroid (*a*). (From Quart. Jr. Microsc. Sci., 1934, lxxvi, 615–646, figures 1, 22, 23.)

(*c*) *Colloid Release as Effected by TA.* Exactly as in spontaneous activation of the thyroid (see figures 1 and 2) so in experimental activation induced by TA-injections one of the most conspicuous processes is the release of the colloid from the lumen of the follicles. This effect was first noticed by Schwartzbach and Uhlenhuth in 1926 and was described in 1928.[6] Later on it was confirmed by Karl Mech and Eduard Uhlenhuth who devised

a technic by means of which an accurate measurement of the colloid content of the thyroid was made possible. In the following graphs the changes in the "colloid level" (i.e. amount of colloid expressed in percentages of total thyroid tissue) and in the cell height are indicated. It will be noticed that TA-injections are followed by an increase in the cell height and a decrease in the colloid level.

In figure 12, taken from the work of Thompson, Mech and Schenthal [28] is shown the effect of discontinuing the TA-injections. Four injections brought the colloid-level down to 8 per cent. After the fourth injection TA administration was stopped; immediately the colloid level began to rise. It is evident that the low colloid level which is the result of the colloid release

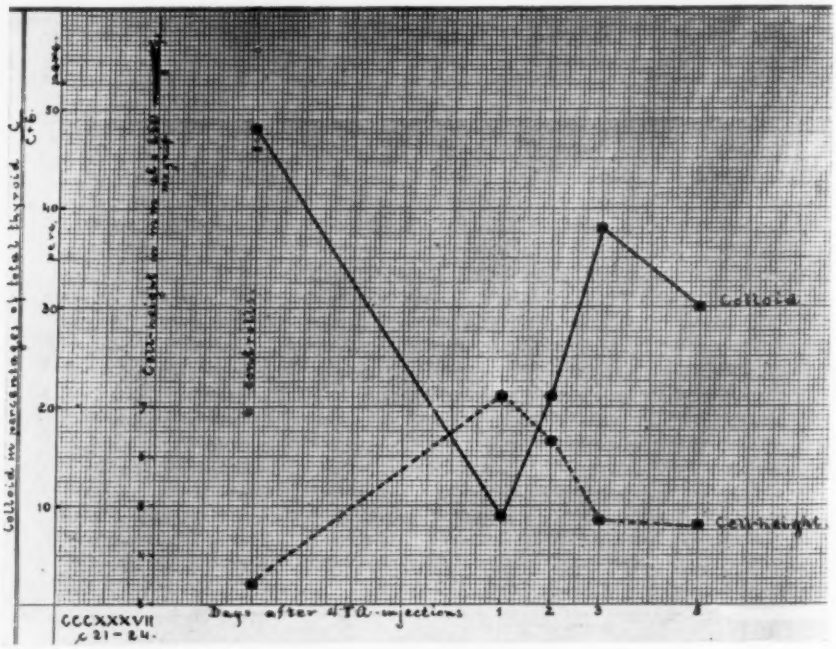

FIG. 12. The drop of the black line indicates the colloid release effected by four TA injections. The rise of this line indicates that the follicles begin to refill as soon as TA-administration is discontinued. The dotted line indicates that the cell height is effected the reverse way. Note the striking agreement between the experimentally activated and the spontaneously activated (figures 2 and 3) thyroids. (Karl F. Mech, Joseph E. Schenthal and E. Uhlenhuth.)

effected previously by TA-injections, cannot be maintained after TA is discontinued. What happens when TA-injections are continued over a longer period is shown in figure 13 (taken from the work of J. Schenthal). At first the colloid level drops rapidly until after the sixth injection it reaches as low a value as can be obtained with the dose employed (50 mg. AL per injection). After this value has been reached, continued injections maintain the colloid level permanently (over a period of three weeks) at this

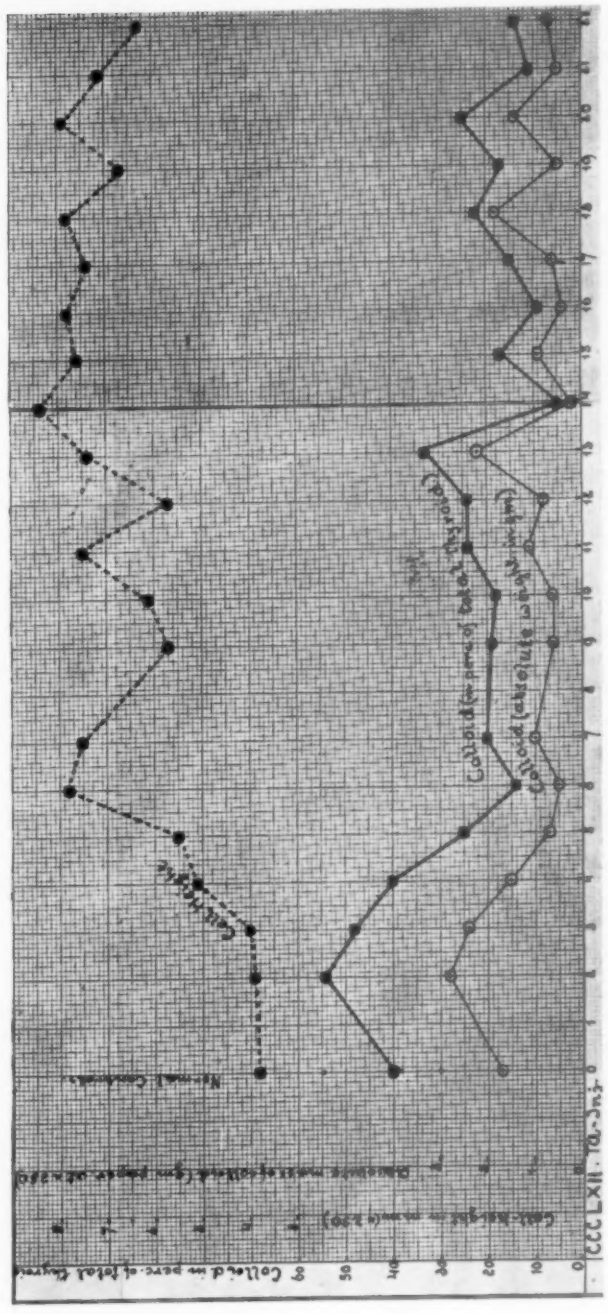

FIG. 13. *Prolonged T.A-injections* in adult salamanders. The low colloid level is maintained and the increased cell height persists. Notice that (in the lowest of the three curves) the absolute weight of the colloid runs very nearly parallel to the colloid percentage; the decrease of colloid is so great and persistent, that even the individual variations in size of thyroids cannot mask it. (Joseph E. Schenthal and E. Uhlenhuth.)

value, but never permit it to rise to the value of the resting gland. Briefly, in our experiments, TA did not lose its efficacy of keeping the colloid level much below its normal value (i.e., at about 25 per cent of the normal colloid level). It will be noticed that the same relation holds true for the cell height which is maintained high throughout the experiment.

From this fact we concluded that at least in respect to colloid level and cell height, we have not felt the need of assuming the action of an "anti-thyreotropic hormone," reported by Collip in his work on warm-blooded animals.

(*d*) *Bodily Changes Resulting from TA-Injections.* (1) We have already mentioned that in the larval aquatic salamander one of the most conspicuous effects of the thyroid hormone is the speedy transformation into an adult terrestrial animal. The same effect is obtained from TA-injections, owing to the release of the thyroid hormone, caused by TA.

(2) Loss of weight.

(3) Severe exophthalmos.

(*e*) *Effect of TA on Metabolism.* (1) As thyroid hormone raises the metabolism, it was to be expected that TA, because of the release of colloid

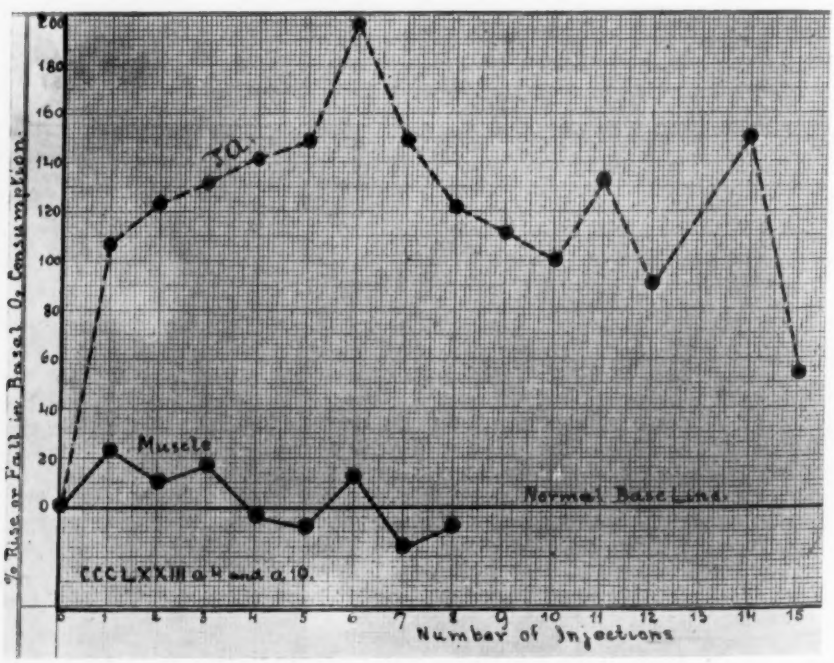

FIG. 14. Thyreoactivator produces a 200 per cent rise in O_2-consumption of the normal adult salamander. (James U. Thompson and E. Uhlenhuth.)

effected by it, would likewise raise the metabolism. Schwartzbach and Uhlenhuth [11, 12, 27] found that in larval salamanders the basal metabolism rises from 30 to 115 per cent above the normal, if TA is injected.

(2) In the adult salamander, Thompson * [29] has shown, in an extensive series of experiments, that oxygen consumption increases up to 200 per cent above normal basal value, if daily injections of TA (equivalent to 50 mg. AL) are made (figure 14). It will be observed from the graph in figure 14, that very much as in Collip's experiments on warm-blooded animals, a peak of oxygen consumption is reached after the sixth injection after which metabolism drops, a condition which has been explained by assuming the gradual development of an antithyreotropic hormone in an animal injected with TA over long periods. In the cold-blooded animal such an assumption is not necessary as the drop in oxygen consumption coincides with the time at which all the stored colloid which can be released at all with a given dose of TA, has been released. It is obvious that after this time the amount of colloid excreted into the blood circulation will be, at least, much smaller than the amount of colloid available before this time as the only colloid available from now on will be the colloid manufactured directly by the cells.

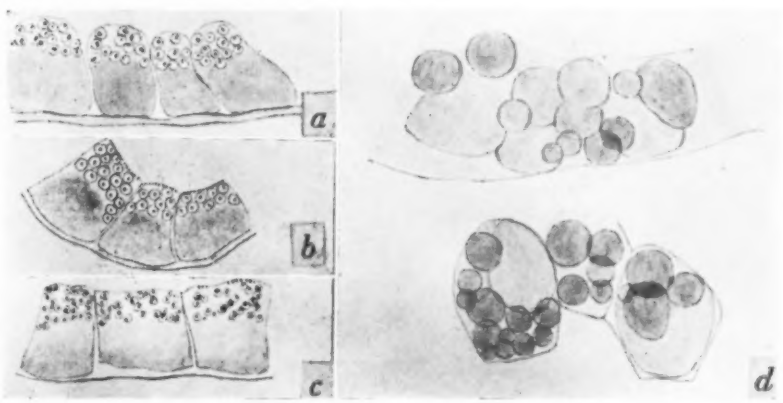

FIG. 15. Injections of acid Ringer solution (*b*) and acid extract of posterior pituitary (*c*) (received 6 intraperitoneal injections of P.L. extracted from P.L. powder prepared under the supervision of Dr. Frederick Fenger of Armour & Co.) do not provoke the appearance of intracellular secretion vacuoles caused by TA-injections (*d*); no change as compared to normal control (*a*). (Guy P. Thompson and E. Uhlenhuth.)

(*f*) *The Power of Activating the Thyroid Is Specific for TA.* At first it was uncertain whether the property of activating the thyroid is specific for A.L. extracts. Large numbers of control experiments were required to test this point.[3,4,7] We obtained the following results:

(1) Neither neutral nor acidified Ringer is capable of effecting the changes of the thyroid gland which are obtained by TA-injections (see figures 15*a*, *b*, and *d*, illustrating experiments by Uhlenhuth and Guy P. Thompson).

(2) Muscle extract has no effect on the thyroid.

(3) Injections of posterior lobe extract are entirely inactive as shown

* The author wishes to express his thanks to Mr. O. G. Harne, of the Department of Physiology of the University of Maryland, for his valuable suggestions and assistance in selecting and constructing the apparatus used for the oxygen determinations.

by Uhlenhuth and Thompson; figure 15 shows that in the adult animal the structure of the thyroid after posterior lobe injections (figure 15*c*) is the same as that of a normal control (figure 15*a*) and entirely unlike that of the thyroid of TA-injected animals (figure 15*d*). As recently it had been reported that thyroid activation may be obtained by posterior pituitary, Harry A. Teitelbaum tested this substance again in large numbers of animals. Again no activation of the thyroid could be secured by extracts made from bovine posterior pituitary either in alkaline, acid or neutral extractives.

(4) Parathyroid extracts prepared exactly like A.L. extracts did not activate the thyroid, as shown by Schwartzbach and Uhlenhuth (figure 16*b*).

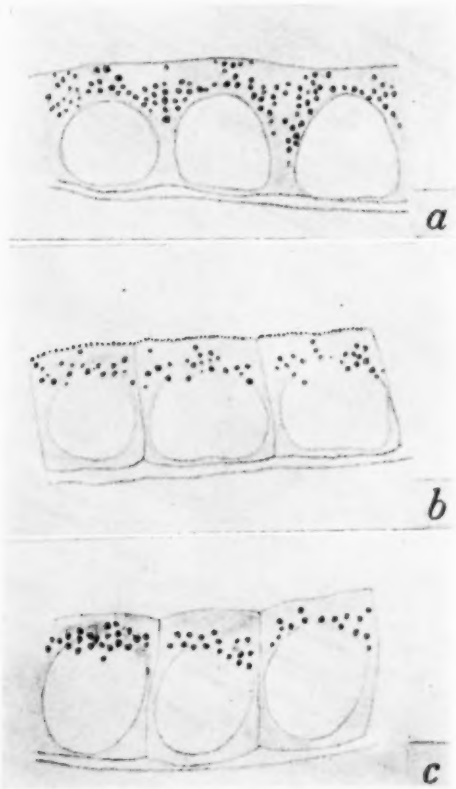

FIG. 16. (*a*) Normal control, Ringer-injected; (*b*) received 4 injections of acid extract of Armour's parathyroid powder; (*c*) received 3 injections of altogether 1 mg. of adrenalin. Neither parathyroid nor adrenalin provokes the formation of secretion vacuoles characteristic of TA effect. (Schwartzbach and Uhlenhuth.)

(5) Adrenalin, a sympathicotonic substance, was administered to large numbers of animals. Although it produces many of the effects well-known from mammalian work, it does not activate the thyroid. This is illustrated in figure 16, from the work on larval salamanders by Schwartzbach and Uhlenhuth. Further data pertaining to this problem will be reported below.

(6) Pilocarpine, a drug which, among other actions, stimulates the parasympathetic nervous system, does not activate the thyroid gland, as shown in figure 17, from work on larval salamanders by Schwartzbach and Uhlenhuth.

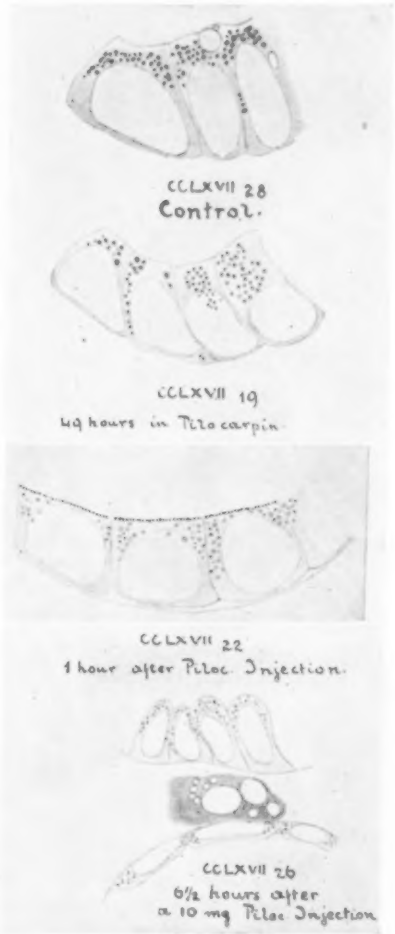

FIG. 17. Neither immersion into pilocarpine nor pilocarpine injections produce any changes in the normal thyroid gland.

(7) Thyroid substance leads to precocious metamorphosis in amphibians and, as in mammals, raises the metabolism of salamanders (shown by James U. Thompson, in as yet unpublished work on adult salamanders); but it does not activate the thyroid. On the contrary it leaves the thyroid entirely dormant, as in the more advanced larval stages (figure 18); or even retards thyroid development, as in early larval stages (figure 19).

(8) Iodine affects the thyroid very profoundly, but it has no resemblance, in its action, to TA. At first it leads to pronounced enlargement

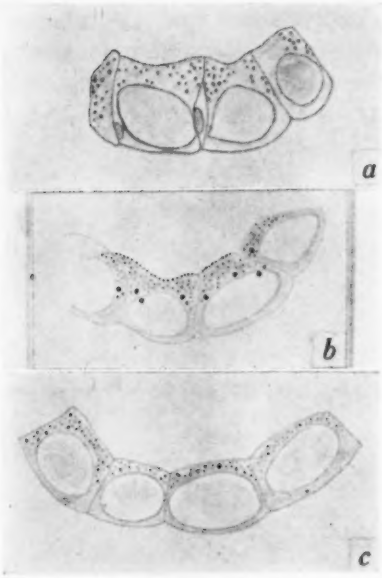

FIG. 18. Effect of feeding thyroid-substance, upon the thyroid-cells, as demonstrated in the fresh thyroid of the tiger salamander by staining vitally the living animal with neutral red. (*a*) Thyroid cells of normal control larva. (*b*) Thyroid cells of a larva which has been under the influence of iodothyrine for 5 days. (*c*) Thyroid cells of an animal which has been metamorphosed by a 12 days action of iodothyrine. Note that the thyroid cells of the animals treated with thyroid substance have failed to progress toward a more active condition; in particular intracellular vacuoles are absent.

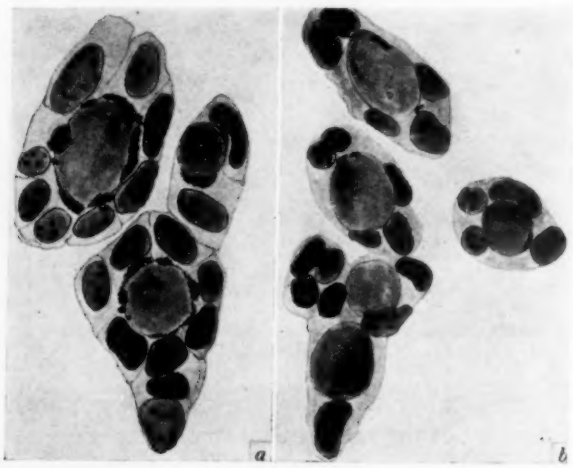

FIG. 19. Effect of thyroid substance (iodothyrine) on larval salamanders, soon after hatching. It enforced metamorphosis before even the limbs were fully developed, but it did not activate the thyroid, nor speed up its development. (*a*) Normal control: early stage of thyroid. (*b*) Thyroid after administration of thyroid-substance. Notice that the follicles are even smaller than in the control, and the cells have not yet attained the same orderly grouping into epithelial walls as they have in the controls.

of the follicles and of the thyroid as a whole owing to increased colloid storage, much as it has been found by David Marine in the mammalian thyroid. Later on it brings about destruction of the thyroid cells and finally disintegration of whole follicles, followed by a decrease in the size of the thyroid and eventually by nearly complete disintegration of the organ [15, 16] (figure 20).

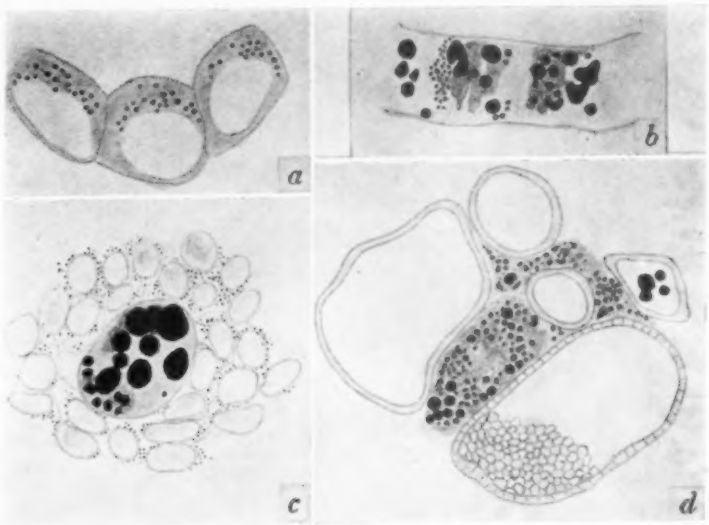

FIG. 20. Destructive effects of inorganic iodine on thyroid cells as seen in salamander thyroids taken from animals stained intravitally with neutral red and examined fresh. (*a*) In the normal gland stainable substance contained in small, evenly distributed granules. (*b*) Advanced lesions after iodine treatment; stainable substance beginning to fuse into lumps. (*c*) Still farther progressed iodine lesions; whole areas in the wall of follicles begin to disintegrate. (*d*) Finally whole follicles are destroyed and disintegrated. (Redrawn from Uhlenhuth and Winter, Roux's Arch., 1929, cxix, 516–530.)

(9) Thyroid substance produces its physiological effects no matter whether it is injected or fed. Much the same is true, in amphibians, for iodized proteins and amino-acids. Anterior pituitary, however, has no effects whatsoever when it is administered orally. It neither raises the metabolism (Schwartzbach and Uhlenhuth) nor does it change the structure of the thyroid gland (figure 21).

(*g*) *Physiological Inactivity of TA in the Absence of the Thyroid Gland.* (1) After complete removal of the thyroid gland the physiological effects obtainable in normal salamanders by TA-injections cannot be reproduced, as shown by Schwartzbach and Uhlenhuth in 1928.[10] It was claimed by Spaul that he could obtain these effects even after thyroidectomy. Figge and Uhlenhuth, in carefully and completely thyroidectomized animals, repeated these experiments,[19, 20] and confirmed the results obtained previously in collaboration with Schwartzbach.

(2) On the other hand, the presence of the pituitary is not necessary

for the production of these physiological effects after TA-injections. In experiments carried out by Frank H. J. Figge, it was shown that in the complete absence of the anterior, posterior and intermediate lobes of the pituitary, a perfect reproduction of the physiological as well as of the structural effects of TA is possible.[20]

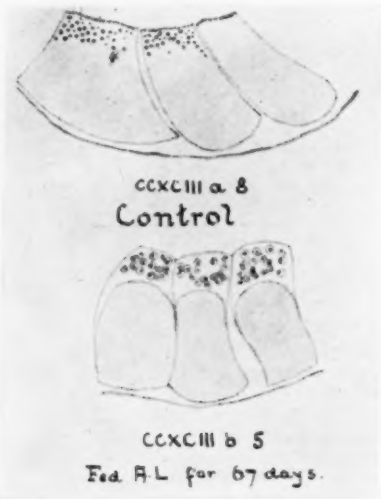

FIG. 21. Oral administration of AL neither has any physiological effects nor does it activate the thyroid gland. Compare thyroid of AL-fed animal (*b*) with thyroid of normal control (*a*). (Schwartzbach and Uhlenhuth.)

(*h*) *Conclusions and Confirmations.* From all the data reported in this article the following conclusions were drawn (1928).

The anterior lobe of the pituitary manufactures a specific substance, the thyreoactivator, which alone among all the substances tested, is capable of activating, in a specific manner, the thyroid gland. By means of the thyreoactivator hormone, the anterior pituitary controls the activity of the thyroid gland.

The essential results submitted in this article were confirmed soon by other investigators and are now generally accepted. Thyreoactivator has been found to activate the thyroid of fishes (Collip), of amphibians (Houssay and collaborators in 1932), of birds (Schockaert 1930), and of mammals (Loeb and collaborators, 1929; Aaron, 1929; Houssay, in dogs, 1932; Collip, 1934).

III. Nervous Excitation of Thyroid Activity

Experienced clinical observers, such as Buschan (1896), F. Chvostek (1917) etc., have placed much emphasis on cases of exophthalmic goiter which developed as a result either of continued grave nervous worries or of sudden severe nervous shocks. Owing to the discovery of the humoral

Figure 22.

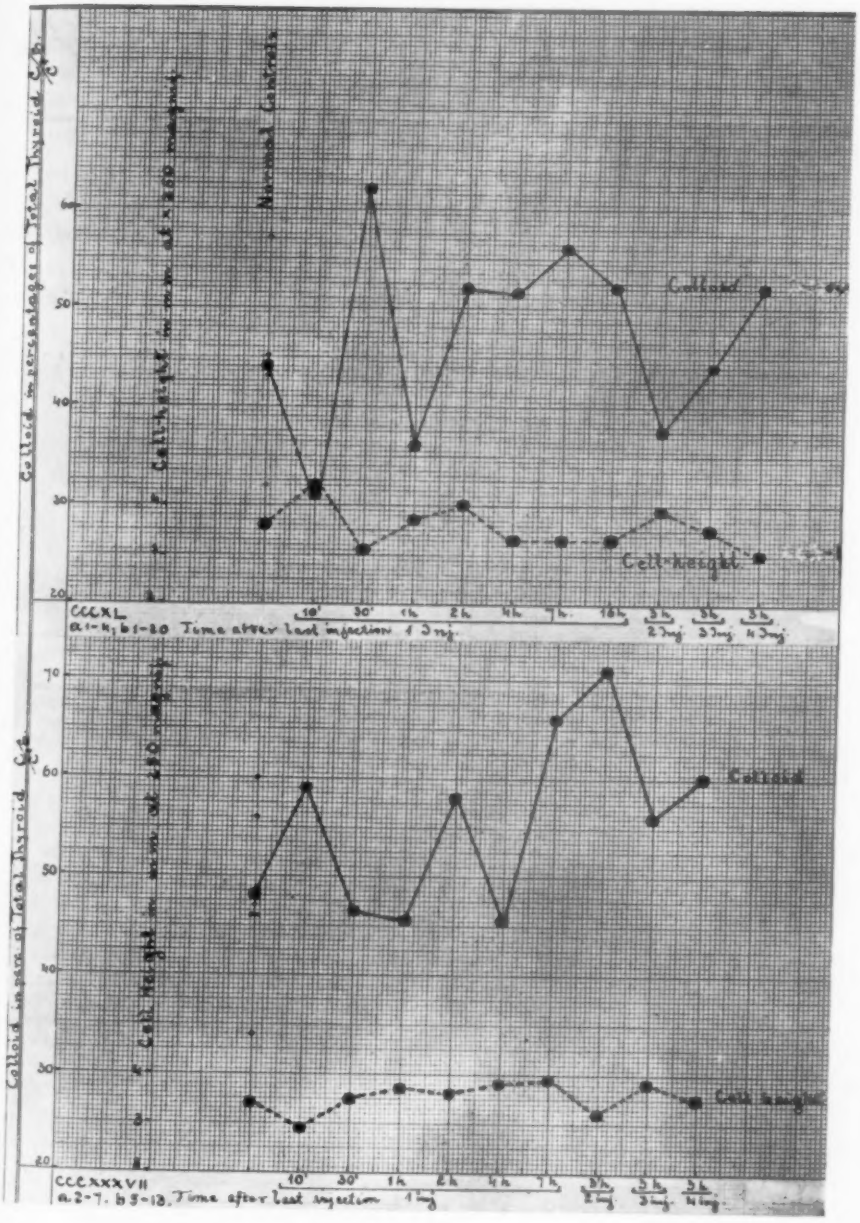
Colloid in mm. of Total Thyroid Cyl.
Normal Controls
Colloid
Cell-height
CCCXL
a.1-4, b.1-20 Time after last injection 1 Inj.
10' 30' 1h. 2h. 4h. 7h. 18h. 3h. 3h. 3h.
2 Inj. 3 Inj. 4 Inj.
Colloid in mm. of Total Thyroid Cyl.
Colloid
Cell-height
CCCXXXVII
a.2-7. b.8-13. Time after last injection 1 Inj.
10' 30' 1h. 2h. 4h. 7h. 3h. 3h. 3h.
2 Inj. 3 Inj. 4 Inj.

Figure 23.

FIG. 22. Adrenalin does not activate the salamander thyroid gland; it neither decreases the colloid content of the thyroid nor does it increase the cell height. (Mech, Schenthal and Uhlenhuth.)

FIG. 23. Pilocarpine does not activate the thyroid gland of salamanders; it neither decreases the colloid content nor does it increase the height of the cells of the thyroid. (Mech, Schenthal and Uhlenhuth.)

excitation of the thyroid gland, interest in the nervous relations of the control of thyroid activity has suffered a setback. It is, however, especially the work of certain noted physiologists, such as Walter B. Cannon and Leon Asher, which offers much encouragement to those who would search for some kind of nervous control, in addition to the humoral control of thyroid activity.

The discovery of the thyreoactivator has opened new roads to a successful attack on the question as to whether or not the nervous system plays any rôle in controlling thyroid activity. Our work along this line is based on the idea that, while stimulation of the nervous system may not activate the thyroid, it may make the gland more responsive to the exciting effects of

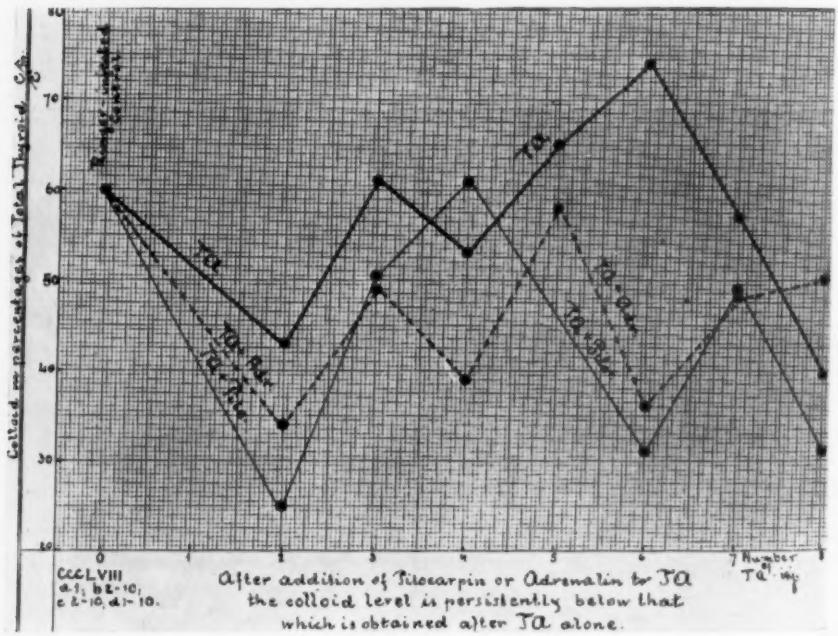

FIG. 24. Adrenalin as well as pilocarpine when injected together with TA, increase the thyroid-activating power of the hormone in salamanders. The colloid content is distinctly more decreased when TA is injected with either adrenalin or pilocarpine than when TA is injected alone. (Edgar van Slyke, James U. Thompson and E. Uhlenhuth.)

thyreoactivator. Our results may be summarized under the following points:

(1) Intraperitoneal injections of adrenalin alone do not activate the adult resting thyroid; they neither decrease the colloid level nor do they increase the cell height in the adult resting thyroid (Mech and Schenthal, figure 22).

(2) Intraperitoneal injections of pilocarpine alone do not activate the adult resting thyroid of the salamander; they neither decrease the colloid

Figure 25.

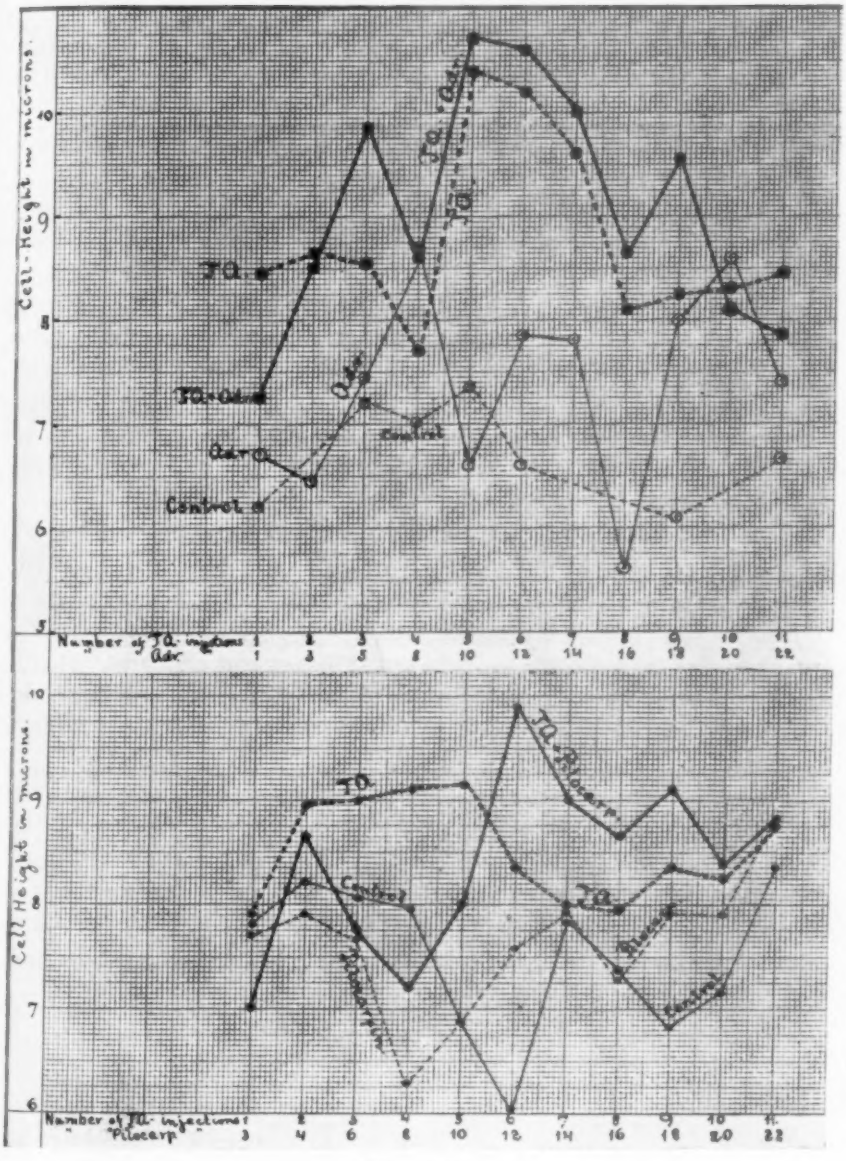

Figure 26.

FIG. 25. In the guinea pig TA combined with adrenalin produces a greater increase in cell height than TA alone, although adrenalin alone has no effect on the cell height of the thyroid. (Teitelbaum and Uhlenhuth.)

FIG. 26. In the guinea pig although pilocarpine alone has no effect on cell height of the thyroid, TA combined with pilocarpine, after the fifth injection, produces a greater increase in cell height than TA alone. (Teitelbaum and Uhlenhuth.)

level nor do they increase the cell height (Mech and Schenthal, figure 23).

(3) Thyreoactivator injections, when combined either with injection of adrenalin or pilocarpine activates the adult resting gland of salamanders more effectively than thyreoactivator alone does; when either adrenalin or pilocarpine is added to TA the colloid level decreases more (figure 24), and the cell height increases more than when TA alone is injected, as shown by Uhlenhuth and Thompson.[24]

(4) These experiments were repeated by Harry A. Teitelbaum[30] in guinea pigs. Again it was found that adrenalin (figure 25) or pilocarpine (figure 26) alone has no effect on cell height. But when adrenalin is injected in combination with TA, the cell height is increased more than after TA alone (figure 25). When pilocarpine is injected in combination with TA (figure 26), it has at first a depressing action on TA effect, but from the sixth injection on, it accentuates the TA effect in raising the cell height. This as well as other differences between the amphibian and the mammal cannot be discussed here in detail; suffice it to mention that they are caused chiefly by differences in dosage and reaction to drugs in general.

(5) To test still further the accentuating effects which adrenalin and pilocarpine evidently have upon the power of TA in raising the activity of the thyroid, the amphibian metamorphosis was used as a method of assaying thyroid activity. It was found that in the presence of pilocarpine (dose 2 mg. per injection) metamorphosis could be obtained with one-half the number (or less), and in the presence of adrenalin (dose 0.05 mg. per injection) with two-thirds (or less) of the number of injections of TA that are necessary to obtain the same effect when TA alone is injected.[23] This result is exactly what would be expected if adrenalin and pilocarpine increase the responsiveness of the thyroid to TA.

(6) Conclusions: While we are not yet in a position to state that the effects we are getting from addition of adrenalin or pilocarpine to TA are caused by the nerve-stimulating properties of these drugs, we have learned that the activation of the thyroid by injections of TA is greatly increased when either adrenalin or pilocarpine is injected in combination with it.

IV. Summary and Conclusions

(1) The anterior lobe of the pituitary manufactures and excretes a specific hormone, the thyreoactivator, which has the power of activating the thyroid gland (i.e., of causing, among other effects, release of the colloid). By means of this hormone the anterior pituitary is enabled to control thyroid activity.

(2) The effectiveness of the thyreoactivator can be greatly increased when either adrenalin or pilocarpine is injected in combination with it.

BIBLIOGRAPHY

1. UHLENHUTH, E.: The elaboration and release of the colloid of the thyroid, Proc. Soc. Exper. Biol. and Med., 1923, xx, 494–496.
2. ——: The essential rôle of the stainable colloid in the specific function of the thyroid, Anat. Rec., 1924, xxvii, 222. (Abstract.)
3. —— and SCHWARTZBACH, S.: Control of the thyroid function by the anterior lobe of the hypophysis, Anat. Rec., 1926, xxxiv, 119. (Abstract.)
4. —— and SCHWARTZBACH, S.: The morphology and physiology of the salamander thyroid gland. II. The anterior lobe of the hypophysis as a control mechanism of the function of the thyroid gland, Brit. Jr. Exper. Biol., 1927, v, 1–5.
5. ——: Die Morphologie und Physiologie der Salamanderschilddrüse. I. Histologisch-embryologische Untersuchung des Sekretions-prozesses in den verschiedenen Lebensperioden der Schilddrüse des Marmorsalamanders, Amblystoma opacum, Roux's Arch., 1927, cix, 611–749.
6. ——: Die Morphologie und Physiologie der Salamanderschilddrüse. IV. Die Sekretions vakuolen und Sekretionskörner in der frischen Schilddrüse des amerikanischen gefleckten Salamanders (Amblystoma maculatum) und des Tigersalamanders (Amblystoma tigrinum), Ztschr. f. Zellforschung und mikroskopische Anatomie, 1928, vii, 595–672.
7. —— and SCHWARTZBACH, S.: Anterior lobe substance, the thyroid stimulator. I. Induces precocious metamorphosis, Proc. Soc. Exper. Biol. and Med., 1928, xxvi, 149–151.
8. SCHWARTZBACH, S. S., and UHLENHUTH, E.: Anterior lobe substance, the thyroid stimulator. II. Effect of feeding anterior lobe upon amphibian metamorphosis, Proc. Soc. Exper. Biol. and Med., 1928, xxvi, 151–152.
9. UHLENHUTH, E., and SCHWARTZBACH, S.: Anterior lobe substance, the thyroid stimulator. III. Effect of anterior lobe substance on thyroid gland, Proc. Soc. Exper. Biol. and Med., 1928, xxvi, 152–153.
10. SCHWARTZBACH, S., and UHLENHUTH, E.: Anterior lobe substance, the thyroid stimulator. IV. Effect in the absence of the thyroid gland, Proc. Soc. Exper. Biol. and Med., 1928, xxvi, 153–154.
11. ——: Effect of anterior lobe substance on basal metabolism in salamander larvae, Anat. Rec., 1928, xli, 25. (Abstract.)
12. ——: Anterior lobe, the thyroid stimulator. V. Basal metabolism, Proc. Soc. Exper. Biol. and Med., 1929, xxvi, 389–390.
13. ——: Anterior lobe and basal metabolism, Anat. Rec., 1929, xlii, 35. (Abstract.)
14. UHLENHUTH, E., and SCHWARTZBACH, S.: Anterior lobe the thyroid activator, Anat. Rec., 1929, xlii, 41. (Abstract.)
15. UHLENHUTH, E.: Die Morphologie und Physiologie der Salamander Schilddrüse. V. Die Wirkung von anorganischen Jod auf die Schilddrüse des Tigersalamanders (A. tigrinum) und des amerikanischen gefleckten Salamanders (A. maculatum), Roux's Arch., 1929, cxv, 184–236.
16. —— and WINTER, C.: Die Morphologie und Physiologie der Salamander-Schilddrüse. VI. Jodimplantation und ihre Wirkung auf die Schilddrüse, Roux's Arch., 1929, cxix, 516–530.
17. UHLENHUTH, E.: The Golgi apparatus in the secretion process of the thyroid gland, Anat. Rec., 1932, lii, 40. (Abstract.)
18. ——: The histology and Golgi apparatus in the activated thyroid of Triturus torosus, Anat. Rec., 1932, lii, p. 86. (Demonstration.)
19. SCHWARTZBACH, S. S., and UHLENHUTH, E.: The morphology and physiology of the salamander thyroid gland. VII. The effect of the thyreoactivator on thyroidectomized animals, Physiol. Zoöl., 1933, vi, p. 236–252.

20. FIGGE, F. H. J., and UHLENHUTH, E.: The morphology and physiology of the salamander thyroid gland. Further experiments on the thyreoactivator, Physiol. Zoöl., 1933, vi, 450–465.
21. VAN SLYKE, E., UHLENHUTH, E., and MECH, K.: A neurohormonal mechanism in thyroid activity, Anat. Rec., 1934, lviii, 41–42.
22. UHLENHUTH, E.: The Golgi apparatus in the thyroid gland of amphibians, in its relation to excretion polarity, Quart. Jr. Micros. Sci., 1934, lxxvi, 615–646.
23. ——, VAN SLYKE, E., and MECH, K.: Nervous control of thyroid activity. I. Effect of pilocarpine and adrenalin on metamorphic action of thyreoactivator, Proc. Soc. Exper. Biol. and Med., 1934, xxxii, 107–108.
24. —— and THOMPSON, J. U.: Accentuation of thyreoactivator effect of anterior lobe by addition of pilocarpine or adrenalin, Anat. Rec., 1935, lxi, 47. (Abstract.)
25. —— and SCHWARTZBACH, S.: Die Physiologie des Thyreoaktivators bei Amphibien. I. Beschleunigung der Metamorphose bei den larven Salamandern, Endokrinologie, 1935, xv, 329–342.
26. ——, SCHWARTZBACH, S., and THOMPSON, G. P.: Die Physiologie des Thyreoaktivators bei Amphibien. II. Die Strukturveränderungen der Schilddrüse der mit Vorderlappen eingespritzten Salamander, Endokrinologie, 1935, xvi, 9–19.
27. SCHWARTZBACH, S., and UHLENHUTH, E.: Die Physiologie des Thyreoaktivators bei Amphibien. III. Erhöhung des Sauerstoffverbrauchs durch Thyreoaktivatoreinspritzungen, Endokrinologie, 1936, xvi, 412–422.
28. UHLENHUTH, E., THOMPSON, J. U., and SCHENTHAL, J. E.: Effect of prolonged thyreoactivator injections on colloid release of the salamander thyroid, Anat. Rec., 1936, lxiv, 52. (Abstract.)
29. THOMPSON, J. U., and UHLENHUTH, E.: Effect of prolonged thyreoactivator injections upon metabolism of adult salamanders, Anat. Rec., 1936, lxiv, 50–51. (Abstract.)
30. TEITELBAUM, H. A., and UHLENHUTH, E.: Effect of adrenalin and pilocarpine upon thyroid-stimulating power of thyreoactivator in guinea pigs, Anat. Rec., 1936, lxiv, 50. (Abstract.)

AURICULAR FIBRILLATION; THE PRESENT STATUS WITH A REVIEW OF THE LITERATURE *

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Auricular fibrillation is a disturbance in the action of the heart, in which the normal contraction of the auricles is replaced by irregular fibrillary twitchings in various parts of the auricular walls. The disorder is believed to arise from a disturbance in the mechanism of the cardiac impulse in which the wave of contraction, instead of following the normal path from the sinoatrial node down the conduction system, pursues a rapid, continuous and irregular course around the mouths of the great veins (circus movement). The resultant fibrillary twitchings, though incapable of causing an effective contraction of the auricles, set in motion innumerable impulses, estimated at four to six hundred per minute, of which only a portion can be transmitted to the ventricles by the conduction system. To this confusion of impulses the ventricles respond with a beat wholly irregular in both time and force and at a rate varying from 100 to 200 per minute (most commonly between 120 and 160), depending upon the integrity of the conducting tissue. Some of the beats are too weak to produce in the peripheral arteries a wave of sufficient magnitude to be perceptible to the palpating finger. The result is a "pulse deficit," the pulse rate at the radial artery being appreciably lower than the heart rate as counted at the apex.

Auricular fibrillation is one of the most important disorders of the cardiac rhythm, and is the commonest type of arrhythmia observed in decompensating hearts. At least 70 per cent of all cases of failure with congestion display this form of arrhythmia (Lewis [1]). "Absolute arrhythmia" (*pulsus irregularis absolutus*), "irregular irregularity," and *delirium cordis* are synonyms indicating the essential clinical characteristics of the condition. The term "perpetual arrhythmia" (*pulsus irregularis perpetuus*), formerly used on account of the belief that fibrillation once established was permanent, now has been abandoned, since it is known that many patients frequently suffer repeated attacks which terminate spontaneously (paroxysmal fibrillation).

History

Although the existence of a condition characterized by an absolutely irregular pulse was known to clinicians for many years, it was not until 1903 that it was first described by Hering [2] as a distinct clinical entity. In 1906 Cushny and Edmunds [3] described a patient with paroxysmal irregularity of the heart and suggested that the irregularity might be the clinical counterpart of auricular fibrillation which they had already observed in their laboratory animals. In 1909 this correlation was definitely established by Rothberger

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and Winterberg,[4] and independently by Lewis.[5] In 1910 Fox[6] and in the same year Mackenzie[7] reported patients with auricular fibrillation in whom no structural defects of the heart could be detected; and in 1913, from clinical and pathological observations on a young subject (aged 23), Gossage and Hicks[8] demonstrated fairly conclusively that this condition can occur in a heart which is normal apart from the fibrillation. In 1914 Wenckebach[9] reported the discovery by a patient that auricular fibrillation was favorably influenced by quinine; and in 1918 Frey[10] showed that quinidine, the dextroisomer of quinine, is the more effective therapeutic agent in this condition. In 1918–1920 Lewis, Feil, and Stroud,[11] and in 1921 Lewis, Drury and Iliescu[12] published their studies which tended to support the concept that the "circus movement" of a contraction wave was the physiological disturbance of the cardiac mechanism in clinical fibrillation. This concept was based originally on the observations of earlier writers, especially those of Mines,[13] Mayer,[13] Garrey,[13] and Levy.[13]

Etiology

In the light of available information no definite etiological factor is recognizable in auricular fibrillation. It is indeed known that auricular fibrillation is most often associated with certain types of heart disease; namely, rheumatic valvulitis, particularly mitral stenosis, and hypertensive heart disease. It is also known that the arrhythmia occurs frequently in hyperthyroid states, with or without other evidence of heart disease. However, less frequently auricular fibrillation has been observed in all other types of cardiac disorder, and in many instances where the heart, apart from the fibrillation, was apparently entirely normal. It occurs at any age, though it is infrequent under the age of 20 years, and is very rare under the age of twelve. The heaviest age incidence is in the third and fourth decades in the valvular group, and in the sixth and seventh decades in the non-valvular group. The sex incidence does not appear to be particularly significant. It has been found to vary widely in different groups of patients. White[14] noted about twice as many males as females showing the arrhythmia; while Cookson[15] found twice as many females as males. Evans[16] in a comparatively small group of cases found a slight predominance of females in the rheumatic patients, and a ratio of three males to one female in the non-rheumatic group. Brown[17] in an analysis of 119 non-rheumatic cases showing auricular fibrillation which came to autopsy, found males predominated over females in a proportion of two to one. However, of the 15 cases in this series which showed no cardiac pathology, 12 were females and three males. In Friedlander and Levine's[18] series of 35 cases of fibrillation without evidence of organic heart disease, there were 32 males and only three females.

Incidence of Associated Heart Disease

Of the various forms of cardiac disorder with which auricular fibrillation is apt to be associated, rheumatic heart disease represents the largest group. Evidence of this form of heart disease is found in more than 50 per cent of all cases of fibrillation. In a recent tabulation of 14 available reports, comprising a total of 2958 patients with auricular fibrillation, Evans [16] found the incidence of rheumatic heart disease to vary from 20 to 69 per cent, or an average of about 49 per cent. In his own group of 39 patients, rheumatic heart disease occurred in 22, or 54 per cent.

Second in importance is the non-valvular or non-rheumatic type of heart disease occurring in relatively elderly people (Cookson [15]; Stroud, Laplace and Reisinger [19]; Levine [20]). There is some disagreement as to the exact nature of the pathological process represented by this group. Levine [20] described it as "the condition called chronic myocarditis in middle-aged or elderly people in whom there is no important disease of the valves but rather some functional or structural damage to the musculature of the heart." Cookson [15] found in this group "no constant associated conditions, except that of age." On the other hand, Brown [17] in his series of 119 cases of this type found that hypertension was the etiological factor in 79.3 per cent of the cases with permanent fibrillation, and in 86.5 per cent of the cases with transient fibrillation. Both Cookson and Brown found coronary disease insignificant as an etiological factor in this arrhythmia. Parkinson and Campbell [21] noted hypertension in 24 per cent and "myocardial disease" in 22.5 per cent of 200 cases of paroxysmal fibrillation. It is possible that some of their "myocardial" patients properly belong to the hypertensive group. Fourteen of those patients showed "gross enlargement of the heart or signs of congestive failure," without evidence of arterial disease or any other etiological factor to account for the enlargement or the congestive failure. It was pointed out by Bell and Clawson [22] that a diagnosis of primary hypertension is justified "in a person suffering from chronic cardiac disease with low or normal pressure, if there is a demonstrable cardiac hypertrophy of the left ventricular type not associated with any disease known to cause hypertrophy." Yater [23] in a study of 145 cases of auricular fibrillation found hypertension a commonly associated condition in the non-rheumatic group. The weight of evidence, therefore, points to hypertension as the clinicopathologic disturbance most often found in the non-valvular type of heart disease associated with fibrillation. This is not an unexpected finding in view of the known importance of hypertensive disease in the causation of non-valvular heart disorders.

The frequent association of auricular fibrillation with thyrotoxicosis has been noted by many observers and is now quite generally recognized.[24, 25, 26, 27, 28] In the 2958 cases of auricular fibrillation, which Evans [16] collected from the literature, the occurrence of thyroid disease ranged between 0 and 44 per cent, with an average incidence of about 9 per cent. In the 200 cases

with paroxysmal fibrillation of Parkinson and Campbell,[21] there were 28 cases or 14 per cent associated with goiter. Obviously the incidence of thyrotoxicosis in this arrhythmia varies with the geographical distribution of goiter.

The nature of the injury suffered by the heart in thyrotoxicosis remains obscure. The majority of opinion holds that no permanent cardiac damage results even though intense hyperthyroidism has existed over a considerable period of time. The whole subject has been comprehensively reviewed in a recent paper by Maher and Sittler.[29] In a series of 180 cases of their own these authors found that " congestive heart failure was not present in uncomplicated thyrotoxicosis. The presence of this phenomenon was associated with the coexistence of a structural lesion. . . . Abnormal cardiac physiologic function as determined clinically or demonstrated objectively by the electrocardiogram, such as heart block (all types), damage to the ventricular conduction system and auricular fibrillation, appeared to be manifestations of primary organic heart disease modified by the element of thyrotoxicosis. . . . The effect of thyrotoxicosis appeared to be that of a catalytic agent. The course of the organic heart disease progressed more rapidly when thyrotoxicosis was active. The thyrotoxicosis brought to the surface latent cardiovascular lesions, which resumed their latency on the successful termination of the thyroid toxemia."

The association of auricular fibrillation with syphilitic heart disease is very uncommon. In his own series of 39 cases with persistent fibrillation, Evans [16] found no instance in which syphilis was present. In the 2958 cases collected from the literature, the incidence of syphilis was approximately 1.5 per cent. Parkinson and Campbell,[21] in their series of 200 cases of paroxysmal fibrillation, found syphilitic aortitis in five instances or 2.5 per cent.

The association of angina pectoris with auricular fibrillation is likewise uncommon. Cookson [15] found only five such cases in a series of 2000 patients with fibrillation. The extraordinary rarity with which angina pectoris is observed in auricular fibrillation tends to support the conclusion of Brown [17] and of Cookson [15] that coronary disease is not a significant etiological factor in this arrhythmia. However, the writer has observed frequently the transient occurrence of fibrillation during the early course of acute coronary thrombosis. This also has been noted by others (Levine [30]).

The relationship between auricular fibrillation and subacute bacterial endocarditis is remarkable. Both conditions are common complications in rheumatic heart disease, but it is well known that they very rarely occur together. High grade mitral stenosis appears to favor the development of fibrillation; bacterial endocarditis is more apt to be engrafted upon a mildly affected mitral valve and upon a deformed aortic valve (Fulton and Levine [31]). In a series of 1200 cases of auricular fibrillation Cookson [15] noted three instances (0.25 per cent) in which fibrillation and infective endo-

carditis were associated. Two of the patients came under observation with both conditions already present. In the third case fibrillation developed just before death. He could find "no example in the literature in which the infection has developed in a patient already under observation with auricular fibrillation."

The Occurrence of Auricular Fibrillation in an Otherwise Normal Heart

Since the demonstration in 1913 by Gossage and Hicks [8] that auricular fibrillation may occur in a heart which is entirely normal apart from the fibrillation, there have been numerous confirmations of this observation. In 1926 Levine [20] reported "several individuals with transient auricular fibrillation and one with the permanent form who, after the most thorough examination, showed no evidence of any disease whatever; the heart except for the arrhythmia seemed entirely normal."

Parkinson and Campbell [21] (1930) found no evidence of heart disease in 30 (15 per cent) of 200 cases of paroxysmal fibrillation. In 12 (6 per cent) of these patients there were "infective" and "toxic" conditions that might have caused the arrhythmia; in the remaining 18 (9 per cent) there was no apparent cause.

Fowler and Baldridge [32] (1930) reported 10 patients in whom auricular fibrillation was the only evidence of cardiac disease. Seven of these were of the paroxysmal, and three of the persistent variety. In one of these patients the "fibrillation was attributed to the removal of cerumen from the external auditory canal, one to exertion, four to alcohol, one to carbon monoxide, one to ether and nitrous oxide anesthesia, and two were in attendance at gasoline stations." One of the patients who fibrillated for two and one-half years, later came to necropsy and "the heart was regarded as grossly and microscopically normal." These authors also collected 35 similar cases from the literature. In the latter the "fibrillation was attributed to such stimuli as electric shock, diseases within the abdomen, emotion and effort, and intoxication by various chemical substances."

Friedlander and Levine [18] (1934) reported 35 cases of auricular fibrillation without evidence of organic heart disease. Of these, 13 were classified as transient, and 22 as permanent. This number represents approximately 6 per cent of all patients with fibrillation seen by them over a period of 14 years. The inciting factors in this group in order of frequency were exertion, gastrointestinal disturbances, alcohol, and upper respiratory infections. In 20 patients there was no ascribable cause.

Orgain, Wolff, and White [33] (1936) reported a similar series of 49 cases of auricular fibrillation without other signs of cardiac disease. This group likewise represents approximately 6 per cent of the total number of patients presenting this arrhythmia seen by them over a period of years. Only three of these cases were classified as permanent, and 46 were of the transient or

paroxysmal type. Two of their cases which came to necropsy presented normal cardiac findings. In many of the cases there were no definite etiological factors. In some the onset of the arrhythmia appeared to "be related to pneumonia, malarial chill, pelvic abscess, alcohol, ether, burns, gall-bladder colic, vomiting, surgical operation, exertion, and emotion." In no instance, however, "when more than one paroxysm had occurred was the same etiologic factor responsible for all or even more than two paroxysms in the same person."

Effect of Drugs and Chemicals on the Induction of Auricular Fibrillation

Drugs and chemicals as primary factors causing fibrillation cannot be considered of great importance. Orgain, Wolff, and White [33] collected from the literature instances in which the occurrence of fibrillation in normal hearts was attributed to epinephrine, digitalis, acetylsalicylic acid, ether, alcohol, tobacco, hydrogen sulphide, arsenic, carbon monoxide, and gasoline fumes. These rare occurrences, however, rather than being regarded as illustrations of specific pharmacological action, may be more logically viewed either as isolated instances of drug idiosyncrasy, or as examples of the "trigger" mechanism suggested by Friedlander and Levine.[18] According to this concept the drug or chemical acts as a trigger upon a heart which, though structurally normal, is yet functionally so altered as to be subject to the sudden inception of auricular fibrillation upon coming in contact with some irritating or exciting agent. The same mechanism is suggested by these authors as a possible explanation of the spontaneous occurrence of fibrillation in certain otherwise normal individuals. In such cases "it is possible that an inherent susceptibility to functional nervous instability provides a fertile field for the propagation and persistence of aberrant stimuli whenever these people are subjected to a particular inciting factor; i.e., emotional strain, acute febrile or toxic disorders . . . the trigger may be related to the adrenal gland."

As secondary factors in initiating fibrillation in definite disease states, the rôle of certain drugs and chemicals appears more clearly established. McEachern and Baker [34] have induced fibrillation by the administration of digitalis in nine patients with cardiovascular syphilis. This is particularly significant in view of the rarity with which fibrillation is ordinarily observed in syphilitic heart disease. Recently Tung [35] reported the appearance of transient auricular fibrillation in 15 patients in association with full or excessive digitalization, and the disappearance of the arrhythmia on the withdrawal of the drug. Twelve of these patients presented gross evidence of heart disease. Of the remaining three, one suffered from mitral valvular obstruction due to a myxoma of the left atrium, and in another there was severe toxemia from suppurative pneumococcal pleurisy. The third pa-

tient was an elderly man (64 years of age) with a carcinoma of the esophagus, atelectasis of the left lung, and displacement of the heart to the left.

Rosenblum, Hahn, and Levine [36] produced transient auricular fibrillation in hyperthyroid animals by the injection of doses of epinephrine too small to alter the cardiac rhythm of normal animals or those with hypothyroidism. Nahum and Hoff [37] have converted a normal heart mechanism into auricular fibrillation by the administration of 0.75 mg. of acetyl-B-methylcholine chloride per kilogram of body weight in four patients with hyperthyroidism, but were unable to induce such changes in normal persons with even larger doses of the drug. They were also able to produce fibrillation by means of the drug in electrically shocked animals. Since the principal action of acetyl-B-methylcholine chloride is vagus stimulation, these investigators conclude that the production of fibrillation in the above described instances was the effect of two distinct factors: (1) a vagus factor (from the action of the drug), and (2) an exciting agent acting on the heart (thyroxine or electric shock), which they designate as the "E factor." In consideration of the above described observations Nahum and Hoff [37] seek to explain the mechanism of clinical fibrillation as involving the interplay of the same two factors. The "E factor" is represented by the stretching of the auricular musculature as in mitral stenosis and in congestive failure, by the overactivity of the thyroid in thyrotoxicosis, and by functional nervous instability in some organically normal hearts. In the presence of any of the above-named states ("E factors"), should overactivity of the vagus develop, or should the individual be abnormally vagosensitive, auricular fibrillation may result. This theory is not incompatible with the "trigger" concept of Friedlander and Levine.

From the above considerations it appears clear that no well defined factor is recognizable as the cause of auricular fibrillation. It seems rather that the development of the arrhythmia is dependent upon the interplay of a number of circumstances which most often arise in the presence of grave heart disease especially in mitral stenosis and hypertension, and in certain toxic states particularly thyrotoxicosis. These circumstances, however, may also arise in apparently healthy states and initiate the arrhythmia in individuals with otherwise normal hearts. The latter group constitutes probably about 4 to 9 per cent of all cases of auricular fibrillation.

Pathology

Yater [23] studied microscopically 29 hearts which had been the seat of fibrillation. From these observations and from a comprehensive review of the literature, he came to the conclusion that there were no specific histologic lesions characteristic of this arrhythmia. This is in agreement with the previously published observations of Frothingham,[38] and similar conclusions have been reached by Cookson,[15] Lewis,[1] White,[14] Brown,[17] Stroud, Laplace and Reisinger,[19] and Friedlander and Levine.[18] Indeed, this now appears to be the generally accepted view.

Types and Frequency of Fibrillation

Fibrillation is classified as (1) persistent, permanent, or established; and (2) as transient or paroxysmal. Both varieties may occur in any type of heart disease or in a heart which is otherwise normal. Furthermore, the transient variety may, after a number of paroxysms, become permanently established. However, mitral stenosis more often favors the establishment of persistent fibrillation, while the transient type is more often associated with the non-rheumatic group and with the otherwise normal heart. Comparatively few statistics which bear on the relative frequency of the two types are available. In White and Jones'[39] series of 376 cases of fibrillation which included 30 patients without other evidence of heart disease, 309 (82.2 per cent) were classified as established, and 67 (17.8 per cent) as paroxysmal. In Kohn and Levine's[40] group of 49 cases, including three cases in which no other heart disease was demonstrable, 46 were classified as permanent fibrillation, and three as transient. (It is not indicated whether the three transient cases were among those with structural heart changes or coincided with the three patients in whom no other evidence of heart disease was demonstrable.) In three small groups of cases including only patients with no other evidence of heart disease the relative frequency of the two types was:

	Permanent	Paroxysmal	Total
Orgain, Wolff and White[33]	3	46	49
Friedlander and Levine[18]	22	13	35
Fowler and Baldridge[32]	3	7	10

Duration of the Paroxysms

In the series of 200 patients observed by Parkinson and Campbell,[21] 160 had paroxysms lasting less than two days. In these the duration of the paroxysms varied from one to 48 hours. In 20 cases the attacks lasted from two to four days, and in eight the paroxysms varied in duration between four and seven days. The remaining 12 patients had paroxysms lasting longer than seven days; some of these attacks continued as long as three weeks.

Orgain, Wolff and White,[33] in their series of 49 patients, noted "great variation in the duration of paroxysms—from the shortest of a few minutes to the longest lasting one year." Usually, however, the paroxysm lasted "a few hours or days."

Friedlander and Levine[18] "arbitrarily" classified the arrhythmia as permanent if it lasted longer than seven days, because "it was assumed that any attack lasting more than a week would not be likely to cease spontaneously."

The above observations appear to justify the conclusion that in the large majority of cases of transient fibrillation (over 90 per cent) the paroxysms do not last longer than seven days; but that in very rare instances a paroxysm may continue for as long as one year and may then cease spontaneously.

Symptomatology

Palpitation is the most common symptom. There may also be exhaustion, breathlessness, faintness, and giddiness. Pain is rarely a complaint. Orthopnea was the first symptom complained of by one patient observed by the author.[41] The onset of the attack may not be accompanied by any particular disturbance, so that the patient may not be aware that the cardiac rhythm has changed. In rare instances the onset is very stormy, being accompanied by intense distress with symptoms of shock, and prostration. In most cases, however, the patients become aware of the sudden onset of palpitation and experience a varying amount of discomfort without complete disability.

Diagnosis

The diagnosis rarely offers any appreciable difficulty. In most cases the existence of the arrhythmia can be diagnosed by means of the palpating finger and stethoscope or naked ear. Levine,[20] quoting Sir Thomas Lewis, gives the following rule: "Given a decompensated cardiac with a heart rate as counted at the apex of over a hundred and a radial pulse that is appreciably less (a pulse deficit of ten or more beats) if the rhythm seems grossly irregular and the pulse is irregular in both time and force the condition is auricular fibrillation nine times out of ten."

The arrhythmia resulting from very frequent, irregularly spaced extrasystoles occasionally constitutes a problem in differential diagnosis. In that condition, as in auricular fibrillation, short, quick beats are followed by compensatory long pauses. However, in fibrillation long pauses also occur frequently after strong beats, a phenomenon not seen in the extrasystolic arrhythmia. Any factor which accelerates the pulse rate (e.g. exercise or atropine) tends to increase the arrhythmia of fibrillation, and diminish the irregularity due to ectopic beats. Conversely, any agent which lowers the pulse rate tends to diminish the irregularity of fibrillation and to accentuate the arrhythmia resulting from extrasystoles. Finally, the diagnosis can be established beyond the possibility of a doubt by means of graphic methods. The disappearance of the auricular wave in the polygraphic tracings confirms the absence of auricular systole. In the electrocardiogram this condition is indicated either by a complete absence of P-waves, or by a succession of rapid, irregular, fundamental oscillations upon which, in turn, still more quivers are superimposed. The ventricular complexes are very irregularly spaced, but are otherwise normal in design except for such changes as may be due to associated disease involving either ventricle.

The Effect of Auricular Fibrillation on Cardiac Function

The effect of fibrillation on cardiac function varies greatly. In some instances, at least for a considerable time, little or no harm appears to result from the arrhythmia, especially if the heart action is maintained at a rea-

sonably slow rate, either by digitalis or by organic heart block without drugs (White[14]). Friedlander and Levine[18] observed a patient who had never received medication and was known to have had persistent auricular fibrillation for 31 years without incapacitating him until five years prior to his death when he developed a left homonymous hemianopsia undoubtedly due to cerebral embolism. Another of their patients "has remained well for years without medication although the rate is always rapid."

In other instances, grave disturbance in cardiac function may follow rapidly the onset of fibrillation, even if no structural changes of the heart can be demonstrated by all available clinical means. Such a case was recently observed by the author.[41] A married woman, aged 43 years, with an excellent past history began to fibrillate without apparent cause. After fibrillating for about three months without treatment she developed severe congestive failure. There was generalized edema with signs of fluid in the serous cavities. Rest and digitalization for one week reduced the heart rate from 160 to 85, produced extensive diuresis with a loss of 15 pounds in weight, and restored compensation to a considerable extent. Roentgen-ray examination disclosed that the pleural and pericardial effusions had largely disappeared and the cardiac shadow was nearly normal. The electrocardiogram showed that the auricles were still fibrillating but that the heart was otherwise normal except for slight changes due to digitalis. A "test" dose of 3 grains (0.2 gram) of quinidine was administered. When the patient was examined two hours later the heart rhythm was found to be normal. Quinidine in half grain doses twice daily was continued for two days. Thereafter all medication was stopped. Within one month the patient resumed her normal mode of life. At this writing, 15 months since the last dose of quinidine, the patient remains entirely well. As nearly as can be determined by all the clinical means available, including roentgen-rays and electrocardiographic studies, her heart is entirely normal.

The only example found in the literature resembling this significant history is that of Case 186 reported by Parkinson and Campbell.[21] These authors point out "how much disability may be produced by fibrillation, apart from any other diseases of the heart."

Between the two extremes just described are found the larger number of patients in whom the arrhythmia causes a degree of cardiac embarrassment which adds measurably to the distress already present in the organic cases, and produces a certain amount of breathlessness and palpitation in those persons whose hearts are otherwise normal. On the other hand, as already pointed out, and for reasons not altogether clear, the presence of auricular fibrillation very greatly reduces the possibility of the development of subacute bacterial endocarditis, and to a considerable extent lessens the severity of the pain of angina pectoris (Cookson[15]).

It is generally accepted that auricular fibrillation predisposes to the formation of auricular thrombi (Kohn and Levine[40]), but that notwithstanding this increased tendency to thrombus formation, embolism is no more com-

mon than when the rhythm is normal (Lewis,[42] Cookson,[15] Kohn and Levine[40]). However, embolism does occur more frequently when after prolonged fibrillation the rhythm changes to normal. Apparently the sudden onset of normal rhythm is an important factor in the production of emboli (Mackenzie,[43] Kohn and Levine[40]).

Prognosis

In patients with fibrillation without other evidence of heart disease the outlook is very favorable. In their group of 49 cases, Orgain, Wolff and White[33] found few cardiovascular changes, "rarely serious and in some instances wholly incidental to the presence of fibrillation. Hyperthyroidism was an uncommon complication. The mortality from auricular fibrillation or from cardiac disease was almost negligible." These conclusions are in agreement with those of Parkinson and Campbell[21] and of Friedlander and Levine.[18] In striking contrast is the unfavorable prognosis held by fibrillators with organic heart disease. The average duration of life in such groups observed by Stroud, Laplace and Reisinger[19] and by Cookson[15] was from two and one-half to seven years. The shortest duration of life was noted in those patients with organic heart disease who began to fibrillate before they reached the age of 20 years. Their average length of life after the onset of fibrillation was less than one year. A comparison of the prognosis in the two chief etiological groups, the rheumatic and the nonrheumatic, revealed no significant difference (Stroud, Laplace and Reisinger[19]).

Treatment

In a recent paper on this subject Kohn and Levine[40] state: "It is indeed questionable whether any form of therapy to restore the normal rhythm is indicated in this condition." This statement must be construed strictly as being applicable only to fibrillation associated with grave organic heart disease, especially rheumatic mitral stenosis; for it is in this type of case that the dangerous untoward effects of quinidine (embolism, collapse, and sudden death) are most apt to manifest themselves. It may be stated, therefore, that in advanced organic heart disease with auricular fibrillation of long standing the best results are usually obtained by adequate digitalization, sufficient to maintain a reasonably slow rate (70 to 80 per minute) and to reduce the pulse deficit to a minimum. In such instances it is probably undesirable to attempt to abolish the arrhythmia by means of quinidine, for the normal rhythm thus established is not likely to be permanent and the benefits derived therefrom are not sufficient to compensate for the risk involved in the use of the drug. On the contrary, occasional cases of organic heart disease with congestive failure appear to derive some advantage from auricular fibrillation since the heart rate may be slowed to more efficient levels with digitalis and the response to that drug is often better than when the rhythm is normal. It also has already been pointed out that auricular

fibrillation reduces very greatly the possibility of the development of subacute bacterial endocarditis and sometimes lessens the severity of the pain in angina pectoris.

Notwithstanding these apparent advantages of auricular fibrillation there are many obvious disadvantages in the continuation of the abnormal rhythm. Perhaps the most important of these is the relationship of the arrhythmia to embolic accidents; for although, as noted above, it is held by some authorities (Lewis,[42] Cookson[15]) that, except under quinidine therapy embolism is no more common in cases with auricular fibrillation than in similar cases with normal rhythm, it is generally accepted that this arrhythmia predisposes to the formation of auricular thrombi. It is also fair to assume that if the auricular fibrillation is terminated shortly after its inception the chances for the formation of such thrombi are greatly reduced. The conclusion therefore seems justified that whenever possible without too great risk, the attempt should be made to establish normal rhythm. In auricular fibrillation of short duration (less than six months) occurring in cases where the organic heart changes are not too far advanced, the dangers attending the use of quinidine are relatively less serious. Hence, in such cases quinidine preceded by digitalization may be used with probable benefit and comparative safety.

The use of quinidine is also worthy of trial in the more advanced cases of chronic heart disease with severe decompensation which fail to respond to digitalis or any other form of treatment. Cases of this type have been reported (Van Nuys[46]; Kohn and Levine[40]) in which quinidine used as a last resort established normal rhythm and restored compensation.

In cases of auricular fibrillation without other evidence of heart disease, quinidine is the most effective therapeutic agent and is the therapy of choice. In such cases dangerous toxic effects from the drug are seldom encountered and the chances of success are further increased by preliminary digitalization (Sollman[47]). After such preparation, a test dose of 0.2 gram of quinidine is administered. In some instances this single "test" dose is sufficient to restore a normal rhythm.[40, 41] If, however, the arrhythmia continues and no untoward effects from the the test dose develop in six to twelve hours, the administration of the drug is resumed in doses of 0.3 to 0.4 gram at four to six hour intervals until normal rhythm is restored or until the appearance of toxic symptoms necessitates the discontinuance of the drug. After the restoration of the normal rhythm, a daily maintenance dose of 0.2 to 0.4 gram or more may be required to prevent recurrence of the arrhythmia. Often the rhythm will remain regular even if the drug is stopped abruptly after the cessation of fibrillation. In this type of case quinidine is almost invariably successful in restoring normal rhythm, and the patient often remains well indefinitely without further treatment.

The total amount of quinidine required to restore normal rhythm varies greatly. As already noted, a single dose of 0.2 gram may be sufficient.

In some instances, however, very large doses up to three or four grams per day may be required (Lewis [1]). Kohn and Levine [40] found no constant ratio between the duration of the arrhythmia, the clinical condition of the patient, and the amount of quinidine necessary to produce a normal rhythm. They found 0.2 gram of quinidine sufficient in one patient with moderate cardiac enlargement and congestive failure, in whom fibrillation was known to have existed for two and one-half months. In another patient, whose arrhythmia was of but a few days' duration, 10.5 grams of the drug were necessary before the rhythm became regular.

In thyrotoxicosis, auricular fibrillation may require no special treatment, since the adequate management of the primary cause often will result in a spontaneous cessation of the arrhythmia. If, in the absence of organic heart disease, such desired results fail to develop within one to three weeks after thyroidectomy, quinidine therapy will usually restore normal rhythm. A resumption of fibrillation after such restoration of regular rhythm usually signifies either that an insufficient amount of the gland was removed, or that some other additional cause was responsible for the arrhythmia.

In hyperthyroidism with normal rhythm, the important indication is the control of the thyrotoxicosis. The early use of iodine, glucose and surgery will tend to prevent the appearance of auricular fibrillation. It is questionable whether quinidine should be used prophylactically in such instances. Statistics bearing on this point are not now available.

The paroxysmal type of auricular fibrillation often requires no special treatment. As already noted, in about 80 per cent of the cases the paroxysms cease spontaneously in less than two days; in many the attacks last but a few minutes to a few hours; and only in very rare instances does a typical attack continue longer than one week (Parkinson and Campbell [21]). In paroxysms of relatively long duration treatment is indicated in accordance with the general principles already outlined. Quinidine in doses of 0.1 to 0.4 gram twice or three times daily may also be used prophylactically in cases subject to frequently recurring attacks.

Auricular fibrillation associated with a slow apical rate not the result of treatment is quite rare and usually signifies the presence of organic heart block. In such cases no special therapy is required apart from the measures indicated by the underlying cardiac condition. However, in the very rare instances where the auricular fibrillation and slow rate are associated with an otherwise normal heart, an attempt should be made to abolish the arrhythmia with quinidine.

Congestive failure is usually significant of grave organic heart disease. However, as has been pointed out above, severe congestive failure may result from untreated auricular fibrillation apart from any other disease of the heart. In such a case quinidine preceded by digitalization may bring about complete and lasting recovery.[41]

Untoward Effects of Quinidine

Kohn and Levine [40] list the following as the most frequent symptoms of quinidine intoxication: "Nausea, vomiting, epigastric distress, diarrhea, headache, palpitation, tinnitus, fear, mental depression, flushing, sweating, syncope, and a feeling of apprehension." They quote Carr and Spoeneman [48] who consider a rise in the pulse rate to 130 as an indication for the withdrawal of quinidine, since such a rise in the rate points to vagal paresis. Skin manifestations such as scarlatiniform rashes and urticaria may occur. The occurrence of embolic phenomena has already been referred to. Sudden death other than of embolic origin is also occasionally observed, possibly due to respiratory paralysis [40] or to ventricular fibrillation.

Treatment of Quinidine Intoxication

The milder symptoms of quinidine overdosage are relieved by the discontinuance of the medication, as the drug is rapidly eliminated by oxidation and excretion.[47] In cases of severe intoxication with symptoms of respiratory embarrassment, life may sometimes be saved by artificial respiration and the intravenous or intracardiac administration of large doses (15 grains) of caffeine sodiobenzoate.[40]

Comparative Effects of Quinidine and Digitalis upon Fibrillation

In properly selected patients quinidine is effective in restoring normal rhythm or in preventing paroxysms in from 70 to 80 per cent of the cases. It is slightly more effective in younger patients (Orgain, Wolff and White [33]). This may be due to the fact that in the older age group, cardiovascular changes are more apt to exist without their being clinically detectable.

Digitalis is useful in slowing the pulse rate and may possibly diminish the frequency of transient attacks (Parkinson and Bedford [49]). However, in established fibrillation, digitalis alone is not effective in restoring normal rhythm (Friedlander and Levine [18]).

REFERENCES

1. Lewis, T.: Diseases of the heart, 1933, Macmillan Company, New York.
2. Hering, H. E.: Analyse des Pulsus irregularis perpetuus, Prag. med. Wchnschr., 1903, xxviii, 377–381.
3. Cushny, A. R., and Edmunds, C. W.: Paroxysmal irregularity of the heart and auricular fibrillation, studies in pathology, 1906, Bullock, Aberdeen.
4. Rothberger, C. J., and Winterberg, H.: Vorhofflimmern und Arythmia perpetua, Wien. klin. Wchnschr., 1909, xxii, 839–844.
5. Lewis, T.: Auricular fibrillation: a common clinical condition, Brit. Med. Jr., 1909, ii, 1528.
6. Fox, G. H.: The clinical significance of transitory delirium cordis, Am. Jr. Med. Sci., 1910, cxl, 815–826.

7. MACKENZIE, J.: Digitalis, Heart, 1911, ii, 273–386.
8. GOSSAGE, A. M., and HICKS, J. A. B.: On auricular fibrillation, Quart. Jr. Med., 1913, vi, 435–440.
9. WENCKEBACH, K. F.: Die unregelmässige Herztätigkeit und ihre klinische Bedeutung, 1914, Engelmann, Leipzig.
10. FREY, W.: Über Vorhofflimmern beim Menschen und seine Beseitigung durch Chinidin, Berl. klin. Wchnschr., 1918, lv, 450–452.
11. LEWIS, T., FEIL, H. S., and STROUD, W. D.: Observations upon flutter and fibrillation, Heart, 1920, vii, 191–245.
12. LEWIS, T., DRURY, A. N., and ILIESCU, C. C.: A demonstration of circus movement in clinical fibrillation of the auricles, Heart, 1921, viii, 361–389.
13. Quoted from Lewis, Feil, and Stroud.[11]
14. WHITE, P. D.: Heart disease, 1931, Macmillan Company, New York, p. 642.
15. COOKSON, H.: The aetiology and prognosis of auricular fibrillation, Quart. Jr. Med., 1930, xxiii, 309–325.
16. EVANS, W. A.: Long-standing cases of auricular fibrillation with organic heart disease; some clinical considerations, ANN. INT. MED., 1936, ix, 1171–1177.
17. BROWN, M. G.: The relationship of coronary arteriosclerosis to auricular fibrillation with special reference to the term "arteriosclerotic heart disease," New England Jr. Med., 1935, ccxii, 963–967.
18. FRIEDLANDER, R. D., and LEVINE, S. A.: Auricular fibrillation and auricular flutter without evidence of organic heart disease, New England Jr. Med., 1934, ccxi, 624–629.
19. STROUD, W. D., LAPLACE, L. B., and REISINGER, J. A.: The etiology, prognosis, and treatment of auricular fibrillation, Am. Jr. Med. Sci., 1932, clxxxiii, 48–60.
20. LEVINE, S. A.: The treatment of auricular fibrillation, Rhode Island Med. Jr., 1926, ix, 19–22.
21. PARKINSON, J., and CAMPBELL, M.: Paroxysmal auricular fibrillation; a record of 200 patients, Quart. Jr. Med., 1930, xxiii, 67–100.
22. BELL, E. T., and CLAWSON, B. J.: Primary (essential) hypertension; a study of 420 cases, Arch. Path., 1928, v, 939–1002.
23. YATER, W. M.: Pathological changes in auricular fibrillation and in allied arrhythmias, Arch. Int. Med., 1929, xliii, 808–834.
24. HAMILTON, B. E.: The heart in toxic thyroid states, Surg. Clin. N. Am., 1924, iv, 1411–1424.
25. DUNHILL, T. P., FRASER, F. R., and STOTT, A. W.: Auricular fibrillation in thyrotoxic conditions, Quart. Jr. Med., 1924, xvii, 326–338.
26. LEVINE, S. A., and STURGIS, C. C.: Hyperthyroidism masked as heart disease, Boston Med. and Surg. Jr., 1924, cxc, 233–237.
27. LAHEY, F. H., and HAMILTON, B. E.: Thyrocardiacs; their diagnostic difficulties, their surgical treatment, Surg., Gynec. and Obst., 1924, xxxix, 10–14.
28. ANDERSON, J. P.: Auricular fibrillation associated with hyperthyroidism, Am. Jr. Med. Sci., 1927, clxxiii, 788–798.
29. MAHER, C. C., and SITTLER, W. W.: The cardiovascular state in thyrotoxicosis, Jr. Am. Med. Assoc., 1936, cvi, 1546–1557.
30. LEVINE, S. A.: Clinical heart disease, 1936, W. B. Saunders Company, Philadelphia.
31. FULTON, M. N., and LEVINE, S. A.: Subacute bacterial endocarditis with special reference to the valvular lesions and previous history, Am. Jr. Med. Sci., 1932, clxxxiii, 60–77.
32. FOWLER, W. M., and BALDRIDGE, C. W.: Auricular fibrillation as the only manifestation of heart disease, Am. Heart Jr., 1930, vi, 183–191.
33. ORGAIN, E. S., WOLFF, L., and WHITE, P. D.: Uncomplicated auricular fibrillation and auricular flutter, Arch. Int. Med., 1936, lvii, 493–513.
34. MCEACHERN, D., and BAKER, B. M., JR.: Auricular fibrillation; its etiology, age incidence, and production by digitalis therapy, Am. Jr. Med. Sci., 1932, clxxxiii, 35–48.

35. Tung, C. L.: Transient auricular fibrillation as a toxic manifestation of digitalis, Am. Heart Jr., 1936, xii, 272–284.
36. Rosenblum, H., Hahn, R. G., and Levine, S. A.: Epinephrine: its effect on cardiac mechanism in experimental hyperthyroidism and hypothyroidism, Arch. Int. Med., 1933, li, 279–289.
37. Nahum, L. H., and Hoff, H. E.: Auricular fibrillation in hyperthyroid patients produced by acetyl-B-methylcholine chloride with observations on the rôle of the vagus and some exciting agents in the genesis of auricular fibrillation, Jr. Am. Med. Assoc., 1935, cv, 254–257.
38. Frothingham, C.: The auricles in cases of auricular fibrillation, Arch. Int. Med., 1925, xxxvi, 437–443.
39. White and Jones: quoted from White.[14]
40. Kohn, C. M., and Levine, S. A.: An evaluation of the use of quinidine sulphate in persistent auricular fibrillation, Ann. Int. Med., 1935, viii, 923–938.
41. Brill, I. C.: Auricular fibrillation with congestive failure and no other evidences of organic heart disease, Am. Heart Jr., 1937, xiii, 175–182.
42. Lewis, T.: Clinical disorders of the heart beat, 1925, 6th edition, Shaw and Sons, London.
43. Mackenzie, J.: Quinidine in auricular fibrillation, Brit. Med. Jr., 1921, ii, 576.
44. Levine, S. A., and Wilmaers, A.: Is quinidine of value in the treatment of auricular fibrillation? Boston Med. and Surg. Jr., 1925, cxcii, 388–392.
45. Brill, I. C.: The treatment of auricular fibrillation and auricular flutter, Northwest Med., 1937, xxxvi, 79–82.
46. Van Nuys, F.: Case report: auricular fibrillation under prolonged quinidine treatment, Boston Med. and Surg. Jr., 1925, cxciii, 673–675.
47. Sollman, T.: A manual of pharmacology, 1932, W. B. Saunders Company, Philadelphia, p. 611.
48. Carr, J. G., and Spoeneman, W. H.: Untoward effects of quinidine, Illinois Med. Jr., 1924, xlvi, 445–449.
49. Parkinson, J., and Bedford, D. E.: The course and treatment of auricular flutter, Quart. Jr. Med., 1927, xxi, 21–50.

"SURGICAL SHOCK" FACTORS IN PNEUMONIA *

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UNDERHILL and his associates [1, 2, 3] did experiments at the time of the World War on the effects of the gases chlorine, phosgene and chlorpicrin. He showed that these lung irritants caused massive pulmonary edema with marked blood concentration. The total extent of this edema was not measured, but it was shown to be a protein-containing exudate. The average increase in blood concentration of four dogs which inhaled 41 to 50 parts per million of phosgene for one-half hour was 166 per cent of the control value as measured by hemoglobin readings. Underhill [4] showed that in the influenzal pneumonia that occurred during the War, a similar pulmonary edema with resultant blood concentration was one of the chief lethal factors. He showed that fluid introduction might be of aid in this condition and that by following blood concentration changes, prognostication was greatly aided. In 11 cases with no complications, nine had a hemoglobin percentage of over 120 with values going up to 140. Moon [5, 6] also noted red counts of 6,000,000 to 8,000,00 with correspondingly high hemoglobin percentages in influenzal pneumonia. He noted at autopsy that there was extreme capillary congestion of the pulmonary and gastrointestinal mucosa, that the lungs were wet and bloody and that frequently there was an effusion of reddish fluid into the serous cavities. Moon and Morgan [7] produced pulmonary edema in dogs by injections of sodium glycocholate with increase in the red count and hemoglobin percentage (2,300,000 and 35 per cent increase respectively in one dog). All of these reports indicate that pulmonary edema may result from both exogenous and endogenous toxic factors.

Underhill [3] analyzed the edematous lungs of animals resulting from inhalation of war gases and found that the water content per unit weight of tissue increased. Sunderman [8] reported that in pneumonia the serum albumin decreased, the globulin increased and the total protein tended to remain within the normal or lower normal limits. Moon and Crawford [9] reported a case of shock syndrome in mercuric chloride poisoning with death 37 hours after taking the poison. In this patient there were 1500 c.c. of blood tinged fluid in the peritoneal and pleural cavities. The lungs weighed 1800 gm. after considerable fluid escaped from them. This means that in the lungs and three major cavities there was an exudation of about 3000 c.c., which if essentially blood and plasma is of great significance.

STUDY OF CASES

Necropsy records of a series of patients dying with pneumonia at the University of Chicago Clinics were studied. Twenty-three such cases were

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used for the present report and the weight of the lungs and presence of pleural fluid noted. These cases represented deaths from lobar, broncho- and terminal pneumonia and in many instances the pneumonia was not the sole cause of death. In these cases the average excess lung weight (assuming normal lungs to weigh 600 gm.) represented 2.45 per cent body weight. In several instances there was appreciable pleural fluid. This brought the total increase to 2.81 per cent body weight as shown in table 1. No chemical analyses were performed, but if this amount represents blood or blood plasma it is of considerable significance.

TABLE I

Increase in Lung Weight and Exudation of Pleural Fluid in Patients Dying with Pneumonia

Case No.	Patient Wgt. Kg.	Duration Disease Days	Excess Lung Wgt. Gm.*	Excess Lung Wgt. as % Body Weight	Pleural Fluid Wgt. Gm.	Pleural Fluid as % Body Weight	Excess Lung Weight + Pleural Fluid as % Body Weight
1	68	2	1850	2.72	—	—	2.72
2	75	4	2230	2.97	—	—	2.97
3	73	7	2640	3.62	—	—	3.62
4	68	long	1200	1.77	—	—	1.77
5	74	short	1020	1.38	—	—	1.38
6	62	3	1290	2.08	—	—	2.08
7	71	9	2370	3.34	800	1.1	4.45
8	61	5	1490	2.44	500	0.8	3.26
9	62	8	2450	3.95	—	—	3.95
10†	64	10	1615	2.52	400	0.6	3.12
11	62	9	1890	3.05	1100	1.8	4.82
12	57	6	1700	2.98	100	0.2	3.16
13	47	7	1130	2.40	50	0.1	2.40
14	56	4	2000	3.57	75	0.1	3.70
15	53	6	1530	2.90	1000	1.9	4.77
16	68	—	1400	2.50	—	—	2.56
17	59	—	670	1.14	600	1.0	2.14
18	76	2	1340	1.76	—	—	1.76
19	68	—	1190	1.77	500	0.7	2.56
20	68	—	1010	1.49	50	0.1	1.56
21‡	72	2	1210	1.67	—	—	1.67
22	37	—	1300	1.89	—	—	1.89
23‡	45	8	1490	1.98	120	0.3	2.24
Average				2.43			2.81

* The excess of the lung weight over the arbitrary normal of 600 gm. is tabulated in this column.

† Blood pressure 142 systolic six days before death.

‡ Blood pressure 130/70 eleven hours antemortem.

EXPERIMENTS

Since no lungs from human pneumonia patients were available for chemical analysis at the time this study was carried out, the lungs of two distemper and one pneumonia dog were analyzed and compared with those of a normal dog. Analyses of the entire lungs were performed and the

nitrogen and protein contents determined on selected portions of the liquid solution of digested lung as shown in table 2, rather than on small bits of solid lung. These analyses show that the nitrogen and protein content in the abnormal lungs is essentially the same as in the normal lungs, indicating that the pneumonic exudate was protein containing. For the sake of more conclusive results the lack of great increase in total weight of these lungs as compared to normal lungs is not helpful. However, in certain instances different portions of the lung (right or left side) were markedly edematous without corresponding dilution of the protein content.

TABLE II

Nitrogen and Protein Content of Normal and Inflammatory Lungs in Experimental Animals*

Dog No.	Condition	Body Wgt. Kg.	Lung Wgt. Gm.	Lung Wgt. as Per Cent Body Wgt.	Lung	Lung Wgt. Gm.	Per Cent Nitrogen	Per Cent Protein
1	Normal control	6.8	132	1.9	Left	51	2.20	13.68
					Right	72	1.98	12.31
					Accessory lobe	9	2.57	16.06
					Average	—	2.25	14.01
2	Pneumonia	20.4	555	2.7	Left	400	1.71	10.68
					Right	115	2.26	14.11
					Accessory lobe	40	2.49	15.56
					Average	—	2.15	13.45
3	Distemper	10.4	147	1.5	Left	58	2.00	12.43
					Right	80	2.17	13.56
					Accessory lobe	9	2.84	17.75
					Average	—	2.34	14.58
4	Distemper	14.7	255	1.7	Left	95	1.92	12.00
					Right	75	1.77	11.00
					Accessory lobe	85	1.92	11.93
					Average	—	1.87	11.64

* These dogs were kindly donated for examination by Dr. O. H. Robertson.

COMMENT

The amount of fluid lost in the various pneumonia cases is extensive, averaging 2.81 per cent body weight. The special significance of loss of this amount of fluid depends on the interval of time during which the loss occurs and on the composition of the fluid. As seen from table 1, death usually occurred several days after the onset of the disease. Since it is difficult to tell whether most of the fluid was lost over the entire course of the disease, or as a terminal phenomenon, the time factor is uncertain. Naturally the loss of considerable blood or fluid in a few hours is of much more serious

import than the loss of a similar amount of fluid over a period of several days. Likewise the composition of the fluid was not determined in any of our cases and only from analogous animal experiments was its plasma-like nature inferred. Furthermore, the presence of shock was not demonstrated in any of the 23 patients as few blood pressure readings were taken. Only two patients had blood pressure readings after entrance and none closer than 11 hours to the time of death.

This quantity of fluid when lost from the circulating blood stream can, however, be of lethal significance. Studies of the amount of plasma-like fluid lost in various other shock-like conditions, both clinical and experimental, indicate a loss of the following amounts: burns 3.2 per cent body weight (Blalock[10]), 2.2 per cent (Harkins[11]); freezing 2.6 per cent (Harkins et al.[12]); release of an extremital constrictor 3.5 per cent (Wilson and Roome[13]); bile peritonitis 2.5 per cent (Harkins et al.[14]); intestinal manipulation 4.5 per cent (Blalock[15]); and plasmapheresis 2.6 per cent (Johnson and Blalock[16]), 4.0 per cent (Harkins and Harmon[17]). No attempt will be made at this time to demonstrate that the loss of this amount of plasma-like fluid was the cause of death in these particular conditions, but the comparison between these figures and the average loss of 2.81 per cent fluid into the lungs and pleural cavities of our patients is pertinent. While this average is at the borderline of the range of fluid loss serious in these other conditions, in several individual pneumonia patients the figure was much higher. To our knowledge little attention has been paid to the possible importance of this fluid loss in pneumonia.

Conclusions

In a series of 23 pneumonia patients there was a combined increase in weight of the lungs and exudation of pleural fluid amounting to 2.81 per cent body weight. Under certain conditions the loss of this much fluid from the circulating blood stream may be significant and a condition resembling surgical shock may possibly result.

REFERENCES

1. Underhill, F. P.: The lethal war gases, physiology and experimental treatment, 1920, Yale University Press, New Haven.
2. Underhill, F. P.: The physiology and experimental treatment of poisoning with the lethal war gases, Harvey Lectures, 1918–1919, pp. 234–255, J. B. Lippincott Company, Philadelphia and London.
3. Underhill, F. P.: The physiology and experimental treatment of poisoning with the lethal war gases, Arch. Int. Med., 1919, xxiii, 753–770.
4. Underhill, F. P., and Ringer, M.: Blood concentration changes in influenza: with suggestions for treatment, Jr. Am. Med. Assoc., 1920, lxxv, 1531–1534.
5. Moon, V. H.: The shock syndrome in medicine and surgery, Ann. Int. Med., 1935, viii, 1633–1648.
6. Moon, V. H., and Crawford, B. L.: Shock syndrome in mercuric chloride poisoning, Arch. Path., 1933, xv, 509–515.

7. Moon, V. H., and Morgan, D. R.: Experimental pulmonary edema, Proc. Soc. Exper. Biol. and Med., 1936, xxxiii, 560–562.
8. Sunderman, F. W.: Studies of serum electrolytes. VII. The total base and protein components of the serum during lobar pneumonia with a note on the gastric secretion, Jr. Clin. Invest., 1931, ix, 615–633.
9. Moon, V. H., and Crawford, B. L.: Shock syndrome in mercuric chloride poisoning, Arch. Path., 1933, xv, 509–515.
10. Blalock, A.: Experimental shock. VIII. The importance of the local loss of fluid in the production of the low blood pressure after burns, Arch. Surg., 1931, xxii, 610–616.
11. Harkins, H. N.: Experimental burns. I. The rate of fluid shift and its relation to the onset of shock in severe burns, Arch. Surg., 1935, xxxi, 71–85.
12. Harkins, H. N.: Shock due to freezing: I. Shift of body fluids and associated blood concentration changes, Proc. Soc. Exper. Biol. and Med., 1934, xxxii, 432–434; Harkins, H. N., and Hudson, J. E.: Shock due to freezing: II. Composition of edema fluid, ibid., 434–435; Harkins, H. N., and Harmon, P. H.: Experimental freezing: bleeding volume, general and local temperature changes, ibid., 1935, 1142–1143.
13. Wilson, H., and Roome, N. W.: The effects of constriction and release of an extremity: an experimental study of the tourniquet, Arch. Surg., 1936, xxxii, 334–345.
14. Harkins, H. N., Harmon, P. H., and Hudson, J. E.: Lethal factors in bile peritonitis. I. Surgical shock, Arch. Surg., 1936, xxxiii, 576–608.
15. Beard, J. W., and Blalock, A.: Experimental shock. VIII. The composition of the fluid that escapes from the blood stream after mild trauma to an extremity, after trauma to the intestines and after burns, Arch. Surg., 1931, xxii, 617–625.
16. Johnson, G. S., and Blalock, A.: Experimental shock. IX. A study of the effects of the loss of whole blood, of blood plasma and of red blood cells, Arch. Surg., 1931, xxii, 626–637.
17. Harkins, H. N., and Harmon, P. H.: Blood concentration produced by plasmapheresis, Surgery, 1937, i, 276–281.

ENCEPHALITIS DUE TO UNDULANT FEVER; REPORT OF FOUR CASES *

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It is a little more than 10 years since undulant fever was recognized in parts of the world remote from the Mediterranean basin. Since then cases have been reported from many parts of Europe, Asia, and this continent. In 1933, 1,787 cases were reported in the United States and it seems highly probable that this was but a small proportion of the true total incidence. Among the complications of the disease the occurrence of meningitis has been described. Hartley, Millice, and Jordan,[1] in 1934, reported a case of meningitis due to undulant fever in which the patient recovered. In their case, there was a prodromal period of four weeks which they suggested could have been due to encephalitis. Krabbe [2] reported a case of meningomyelitis due to Bang's disease but made no mention of a true encephalitis.

We wish to present four cases of encephalitis in one of which features highly suggestive of hypothalamic and pituitary damage were present. In all the cases, the agglutination test or skin test indicated that undulant fever was present and in all no other etiological factor could be demonstrated. So far as we have been able to discover, this clinical manifestation of the disease has not been reported previously in the literature.†

Case Reports

Case 1. The patient was a boy 14 years of age who had been well until four weeks before admission to the hospital. At that time he had an influenza-like infection and missed two weeks of school. When he returned to school, he felt much below par and did not take an active interest in school activities. The day before admission here, he complained that he could not see well and a severe headache developed.

Physical examination revealed a slight fever and marked choking of both optic discs with blindness in the right eye and very little vision in the left. The boy could not see well enough to permit study of the visual fields. Neurological examination and roentgenographic studies of the head revealed no other abnormalities A lumbar puncture was done which showed an initial pressure of 190 mm. of water with normal dynamics. Examination of the spinal fluid revealed findings which were not abnormal. The leukocyte count in the blood varied from 5,000 to 11,000 and the differential counts were normal.

Five days after admission, the patient complained of a generalized, severe headache and on that day he vomited. The fever continued to be present. Bilateral positive Babinski signs were present. An encephalogram revealed no abnormalities.

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From the Cleveland Clinic, Cleveland, Ohio.

† Since these cases were collected, we have been interested in three cases of undulant fever associated with papilledema reported by Rutherford.[3] He does not emphasize the presence of encephalitis as much as we have done, but we feel that all these cases fall into the same group.

The diagnosis at this time was encephalitis, but since the appearance of the optic discs indicated increased intracranial pressure, a right subtemporal decompression was done in an effort to restore the patient's vision. The decompression did not bulge postoperatively. The fever persisted, varying daily between 97.7° and 103° F. and occasionally rose as high as 104° F. An agglutination test for undulant fever was done and was found to be positive in a dilution of 1:640.

Numbness of the legs and retention of urine developed, and in view of the previous findings the diagnosis was changed to encephalomyelitis. The vision began to return, the neurological signs began to diminish, and the patient was discharged on the twenty-ninth postoperative day. The temperature was 101° F.

Thirty days after his discharge from the hospital, the patient's temperature was normal but he was still weak. Two months later his vision had returned and he was free from symptoms and signs insofar as his original illness was concerned.

This boy, who lived on a farm, had consumed much raw milk; his father was found to have a positive undulant fever agglutination test.

Case 2. A woman 55 years of age was admitted to the Clinic in April 1934, complaining of "headaches and vomiting." Seven months before admission, fever and chills had been present for four weeks and no cause was found. Two months before admission, similar symptoms had been present for 10 days and at this time, headaches and vomiting began which did not stop. She was in a hospital elsewhere for one week and was in a stupor during that time. A lumbar puncture had showed no abnormalities.

The patient entered the hospital for observation. Roentgenographic studies of the head, chest, kidneys, ureters, and bladder revealed no abnormalities. No evidence of tuberculosis could be found by roentgen examination or culture from voided and bladder urine. There was a slight haziness of the optic discs but the visual fields showed no changes. Lumbar puncture revealed no abnormal findings. The initial spinal fluid pressure was 170 mm., and following removal of 6 c.c. of spinal fluid was 110 mm. of water. The total protein was 20 mg. and no globulin or cells were present. There was a suggestive bilateral digital reflex. It was noted that a slight fever was present while the patient was in the hospital. A diagnosis of mild encephalitis was made and she was allowed to go home.

The patient was readmitted for study and recheck 10 months later. The headaches were still present but less severe. The vomiting had ceased but there was some nausea, and the temperature rose to 100° F. each day. Undulant fever agglutination tests were negative but an intradermal test using 0.1 c.c. of Brucellin was markedly positive, and with this test the temperature rose to 100.5° F. Culture from a duodenal drainage revealed diphtheroid bacilli and yeast but no organisms of undulant fever. The positive reaction of the intradermal test in our opinion established the diagnosis of chronic undulant fever as the only demonstrable cause of this patient's symptoms.

Case 3. The patient was a young married woman 25 years of age who entered the Clinic May 24, 1934, complaining of fatigue, gain in weight, and scanty menstruation which had been present for two years. The onset of her symptoms occurred one and one-half years before this examination with an acute illness which was characterized by fever and extreme exhaustion, and the patient had never been well since that time. Somnolence became a very bothersome symptom; she had difficulty in awakening before noon each day and her previously excellent memory had become poor. Exhaustion had been so severe that bed rest was necessary for one or two weeks at a time. No headaches, diplopia, polydipsia, or polyuria were present. Libido began to decrease slowly until sexual desire was completely gone. About 25 pounds in weight had been gained. Menstrual periods had begun at the age of nine but had been irregular until the age of 14 when they became regular.

A fairly normal pregnancy terminated eight months before our examination. Six weeks after delivery, the periods began again but they had become more scanty each month until at the time of our examination, very scanty menstrual flow occurred for part of one day each month.

Physical examination revealed a woman 61.5 inches tall who weighed 145 pounds. The temperature and pulse rate were normal and the blood pressure was 98 mm. systolic and 70 mm. of mercury diastolic. The distribution of body fat was of the cerebral type. The optic discs were hazy but examination of the visual fields revealed them to be within normal limits. No clinical signs of hypothyroidism were present. Laboratory study revealed the urine to be normal as was the blood except for 45 per cent lymphocytosis. Complete blood chemistry examination revealed no abnormalities except in the level of the cholesterol which was 231 mg. per 100 c.c. A glucose tolerance test was done using 100 grams of glucose orally. Blood sugar determinations fasting one-half, one, two, and three hours following glucose administrations were 88, 117, 105, 84, and 78 mg. per 100 c.c. The basal metabolic rates averaged minus 12 per cent. Roentgenograms of the head revealed no evidence of pathological change and dental roentgenograms revealed no evidence of infection.

Bio-assays revealed a positive Friedman test which was probably due to antuitrin-S (pregnancy urine prolan) which had been administered until four days before admission. Assay for urinary estrin by the Kurzrok method on a 24 hour specimen of urine showed 3.4 and 4.0 rat units on two examinations.

Hypothalamic damage was indicated because of the rather marked weight gain which took place in the presence of fever, the fact that it was distributed as in pituitary or cerebral disease and because of the excessive somnolence which occurred. Damage to the pituitary region was strongly suggested by the marked diminution in libido and by the occurrence of hypomenorrhea. The metabolic rate and glucose tolerance were not decidedly abnormal but were consistent with some damage to these structures.

A diagnosis of pituitary hypothalamic syndrome following encephalitis was made which corroborated the diagnoses not then known to have previously been made separately by Dr. W. James Gardner and Dr. Louis J. Karnosh.

After 10 months, no improvement was found and Dr. Frank J. Geib suggested that the condition might be due to undulant fever. The agglutination test was positive in a dilution of 1:60 and severe reactions occurred after the administration of undulant fever vaccine in amounts less than 0.5 c.c. Further investigation of the temperature showed that fever recurred at regular intervals. For from 16 to 17 days, the patient would be free from fever, then for eight days fever would be present, only to disappear for about 16 days again. The symptoms were all aggravated during the period of fever.

With our knowledge of the preceding cases, we felt that it was logical to presume that undulant fever caused this patient's symptoms. Undulant fever vaccine was administered and one year later the patient was somewhat improved, but some reaction still occurred after the use of the vaccine and fever recurred at regular intervals. During the periods when the patient was free from fever, there was little local or general reaction to vaccine, but both local and general reactions increased during the febrile period.

Case 4. The patient was an unmarried woman 31 years of age who complained of diplopia, headache, and staggering gait. She had been well until eight years before this examination when menstrual irregularity developed which was associated with considerable excitability. That year a partial oöphorectomy was performed with no immediate change in the menstrual cycle. Later, the periods slowly became more frequent and more prolonged. It was not long after the operation until the patient had a "nervous breakdown" which lasted most of the year. Fairly frequent attacks

of fever occurred and during these attacks she was confined to bed. Her symptoms then disappeared except for the menstrual irregularity.

Seven years after the onset of the first symptoms, the patient began to be extremely excitable again, and this was accompanied by persistent diplopia. The nervousness became so severe that she was confined to a sanatorium for five weeks but showed no improvement. Later, drowsiness progressed to coma and she was confined to the hospital for three weeks. The temperature varied from 105° to 107° F., and the neurologist in charge made a diagnosis of encephalitis. The patient was discharged from the hospital. At the time of discharge she weighed about 60 pounds. The coma and somnolence subsequently disappeared and her weight increased to 125 pounds.

One year later, in the summer of 1935, the patient again began to have severe headaches with marked persistent diplopia. The gait was staggering and there was distinct static ataxia. The diplopia was relieved with prisms but monthly examination of the visual fields showed a marked and progressive concentric diminution of the entire field. Undulant fever agglutination tests had given negative findings.

The patient reëntered the hospital in December 1935. General physical examination revealed no abnormalities except those mentioned above. The basal metabolic rate was minus 11 per cent, the blood Wassermann was negative, the urine was free from sugar, albumin, pus, and casts with a daily output of approximately 2,000 c.c. The hemoglobin was 12.5 grams per 100 c.c. of blood; the red blood cells numbered 5,200,000, the leukocytes numbered 7,500 with 40 per cent lymphocytes. The daily temperature was about 99.4° F. Roentgen examination of skull and chest showed no abnormal changes. Lumbar puncture showed a spinal fluid pressure of 80 mm. of water with normal dynamics. The cell count was 4 with a negative Wassermann reaction.

An undulant fever skin test with 0.05 c.c. of undulant fever vaccine (Jensen-Salsbery) was markedly positive, producing an abscess after 72 hours. This sloughed, then healed after 10 days. Vaccine therapy was instituted with marked local and systemic reactions.

Diagnosis: Chronic undulant fever encephalitis.

Discussion

The relationship between encephalitis and undulant fever first was suspected in the first case and this was proved insofar as was practicable. In the second case, the diagnosis of encephalitis was made 10 months before undulant fever was suspected as the etiological factor. In the third case, decreased menstrual flow was associated with somnolence and other evidence of hypothalamic damage.

Since we have depended to a rather large extent on a markedly positive intradermal test for the diagnosis in two of our cases and since this method has not been as widely used as the agglutination test, we wish to explain why we consider that such a diagnosis is warranted.

Cutaneous hypersensitiveness to *Brucella abortus* has generally been considered by those who have investigated it as a good criterion in the diagnosis of undulant fever. However, it need not necessarily be considered as evidence of active infection. From the work which has a direct bearing on this point, the following reports in the literature may be cited: In 1918, Fleischner and Meyer [4] showed that infection of guinea pigs with *Bacillus abortus bovinus* always produces cutaneous hypersensitiveness. In 1929, Giordano [5]

reported that the intradermal injection of a suspension of killed *Brucella abortus* yielded unmistakably positive reactions in 25 known cases of undulant fever and gave negative results in 99 of 100 controls. Levine [6] in 1931 reported the results of intradermal tests in 365 individuals. Using suspensions of *Brucella abortus* antigens, cutaneous hypersensitiveness was shown in 27 cases and in only four of these was there no history of undiagnosed illness.

Yeckel and Chapman [7] in 1933 reported the results of 250 intradermal tests in which killed bacterial suspensions of *Brucella abortus* were used. Fourteen definitely positive reactions were obtained and in only one instance was there no history of possible undulant fever. These workers concluded that, in the presence of a negative agglutination reaction, the intradermal reaction may be positive and thus lead to a definite diagnosis. Goldstein [8] found 26 positive cutaneous reactions to saline suspensions of *Brucella abortus* among 253 unselected cases in an area where undulant fever was prevalent, and 13 of these patients gave histories indicating possible sources of infection with *Brucella abortus*. Favorite and Curtis [9] found positive skin tests in 10 known cases and only one positive reaction was obtained in testing 90 controls. A subsequent history in this one case was very suggestive and the patient was shown to have an agglutination titer of 1:250.

In our own series of 90 unselected cases in which a tentative clinical diagnosis of undulant fever had been made, the skin test was performed 55 times. In 29, the intradermal reaction was definitely positive despite negative agglutination tests.

We have seen two cases in which the skin test was negative, yet positive undulant fever agglutination was found in testing the sera. In neither was there a definite clinical diagnosis and there were other extenuating circumstances. In the first case, the agglutination titer was only 1:10 and autopsy showed the presence of miliary tuberculosis. In the second case, the agglutination test was positive in one laboratory but negative in another. Blood cultures and opsonic activity [10] have not been determined in our cases.

In the intracutaneous tests reported here, with the exception of Case 2, 0.05 to 0.1 c.c. of Jensen-Salsbery undulant fever vaccine has been used. This contains a heat killed suspension in normal saline of *Brucella melitensis*, variety *abortus* and *suis*, 50 per cent of each preserved with 0.5 per cent phenol. Each cubic centimeter contains six billion killed organisms. In Case 2 Brucellin was used. The Brucellin used in this test was made in Huddleston's laboratories where it was developed by Hershey. It is a soluble nucleo-protein fraction of the three species of Brucella in 1:1000 dilution in slightly alkaline physiological salt solution.

The area of redness resulting from such an injection may be from three to seven centimeters in diameter and occasionally larger. It is edematous, hot, and tender and at times lymphangitis, adenitis and fever may be present. In some cases, a necrotic core or abscess forms and, in many patients, healing takes place slowly, leaving an area of pigmentation which remains for

many weeks. Those intradermal reactions which disappear within two days may be considered to be of little significance.

In evaluating the significance of such a reaction, the history of the patient must be considered. In addition, it is frequently of significance that small doses of vaccine, which are given for therapeutic purposes, produce unusually great responses in temperature. Where other causes for fever and accompanying symptoms can be eliminated and, in the presence of a strongly positive intracutaneous reaction, we believe a diagnosis of undulant fever is warranted.

Two patients (Cases 1 and 2) have shown improvement without specific treatment. The third patient failed to improve without specific treatment but has shown some improvement since it has been instituted. While there is improvement at present in the condition of the fourth patient, her prognosis seems uncertain in view of the history. While the authors realize that the evidence presented above does not constitute proof that encephalitis in these cases was actually caused by growing undulant fever bacilli in the perivascular spaces or nervous tissue of the brain and cord, the findings are nevertheless highly suggestive that such was the case.

Summary

1. Four cases of encephalitis have been presented.

2. The etiological factors have apparently been the organisms of undulant fever as determined by agglutination tests in two cases and by intracutaneous tests in the other cases.

3. In one of the cases, evidence suggestive of hypothalamic or pituitary damage was present.

References

1. Hartley, G. A., Millice, G. S., and Jordan, P. H.: Undulant fever meningitis: report of case with recovery, Jr. Am. Med. Assoc., 1934, ciii, 251–253.
2. Krabbe, H. H.: Meningomyelitis due to Bang's disease, Rev. Neurol., 1934, i, 34–38.
3. Rutherford, C. W.: Papilledema in undulant fever: report of cases, Jr. Am. Med. Assoc., 1935, civ, 1490–1492.
4. Fleischner, E. C., and Meyer, K. F.: The bearing of cutaneous hypersensitiveness on the pathogenicity of the *Bacillus abortus bovinus*, Am. Jr. Dis. Child., 1918, xvi, 268.
5. Giordano, A. S.: *Brucella abortus* infection in man, the intradermal reaction as an aid in diagnosis, Jr. Am. Med. Assoc., 1929, xciii, 1957–1958.
6. Levine, W.: The intradermal test as an aid in the diagnosis of undulant fever, Jr. Lab. and Clin. Med., 1931, xvi, 275–281.
7. Yeckel, H. C., and Chapman, O. D.: Brucella (alcaligenes) infections in man, the intradermal reaction as an aid in diagnosis, Jr. Am. Med. Assoc., 1933, c, 1855–1856.
8. Goldstein, J. D.: Cutaneous reactions in the diagnosis of undulant fever, Jr. Clin. Invest., 1934, xiii, 209–218.
9. Favorite, G. L., and Curtis, F. D.: The intradermal test in undulant fever, Jr. Lab. and Clin. Med., 1935, xx, 522.
10. Huddleston, I. F., Johnson, H. W., and Hamann, E. E.: The study of opsonocytophagic power of blood and allergic skin reaction in Brucella infection and immunity in man, Am. Jr. Pub. Health, 1933, xxiii, 917–929.

NONVALVULAR HEART DISEASE UNDER THE AGE OF FORTY-SIX YEARS *

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INTRODUCTION

NONVALVULAR heart disease, often misnamed "myocarditis," is generally regarded as a condition of degenerative nature in older patients, attributable to coronary sclerosis or hypertension or both. That it may be frequently found in youth is not well known, nor are the etiological factors behind it generally appreciated.

Because of the interest and obscurity of youthful nonvalvular heart disease, we have undertaken to review a large number of cases in the pathological records of the Massachusetts General and Boston City Hospitals, focussing our attention upon the myocardial lesions which were reported. We have limited the study to younger patients and so have arbitrarily excluded those cases over 45 years of age, in order to reduce the preponderance of coronary sclerosis and hypertensive heart disease that might mask other conditions. The more recent years were chosen because the necropsy records were more complete. The cases reviewed all came to autopsy between the years 1920 and 1933. In selecting the cases we have included all those with hearts showing no valvular deformities or congenital defects, but with muscle injury recent or healed, or increase in heart weight to 350 grams or more in women and to 375 or more in men. For children we accepted the figures given by Vierordt and Müller [6] as the normal range.

Birth	20 to 25 grams	2 years	45 to 55 grams
1 month	15 to 20 grams	4 years	65 to 75 grams
6 months	20 to 25 grams	8 years	95 to 105 grams
1 year	30 to 40 grams	12 to 16 years	150 to 250 grams

In the course of this study we have reviewed 4,531 cases in the records of the Massachusetts General (2,600) and Boston City Hospitals (1931). From this group 250 cases were selected which fulfilled the requirements stated above. The pathologic reports were studied with special reference to cardiac findings, although in many instances the description was limited to a routine gross examination. The work was supplemented by a survey of the clinical records of the cases selected from the pathological reports, with particular emphasis on such points as duration of the disease, degree of hypertension, anemia, and clinical and laboratory data. The material has been combined in the appended charts and will be discussed in detail under appropriate sections.

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Undoubtedly the most accurate way of estimating the weight of the normal heart is through the use of Smith's [2] coefficients: 0.43 per cent of body weight for men and 0.40 per cent for women. However, since the weight of the patients was not regularly included in the clinical records, the method was not applicable in this instance. The limits of heart weight up to 350 grams for women and 375 grams for men, chosen at the advice of Dr. Tracy Mallory of the Pathological Department of the Massachusetts General Hospital, were placed somewhat higher than most estimates to compensate for the small amount of aorta (at the most 20 grams) which is included in weighing the heart.

In spite of the most careful examination of clinical records, it is impossible to exclude a past hypertension of which there is neither history nor evidence at the time of examination. In several of the cases selected the size of the heart seemed out of all proportion to any initiating cause that we could find. When the blood pressure readings consisted only of a single determination with the patient in congestive failure, it can hardly be said that hypertension had been excluded as a cause. However, the number of cases in which this probability existed was not very large, though the source of error must be taken into account in evaluating the results.

Details of the Present Study

Of the 4,531 necropsy records reviewed, 250 cases, or 5.5 per cent of the total number, were found to belong to the group which we have outlined. The pathological condition which was most commonly associated with myocardial abnormality was hypertension, frequently accompanied by nephritis, with acute and chronic infections a close second. The complete classification is given in table 1.

Table I

		Cases
1. Hypertension		97
(*A*) With nephritis	67	
(*a*) Chronic nephritis	62	
(*b*) Acute glomerulonephritis	5	
(*B*) Without nephritis	14	
(*C*) With other conditions	16	
2. Acute and chronic infections		91
3. Blood disorders		27
4. Coronary occlusion		5
5. Congenital idiopathic hypertrophy		4
6. Hyperthyroidism		1
7. Cardiac failure of unknown etiology		8
8. Miscellaneous		17
Total		250

The highest incidence of these myocardial abnormalities was found in the group from 41 to 45 years of age, and the lowest from 11 to 15 years of age. Starting with a fairly high incidence in the first five years of life, there was a steady decline in incidence until the fifteenth year, following which there was a gradual rise. This variation is perhaps explained by the

progressive decline in acute infections of childhood up to the fifteenth year, and by the steady increase in other forms of heart disease after that time. Males predominated almost in the ratio of two to one (162 to 88). The age incidence for both males and females is given in table 2.

TABLE II

Age group (years)	Number of males	Number of females	Total
0 to 5	16	5	21
6 to 10	7	4	11
11 to 15	1	3	4
16 to 20	8	6	14
21 to 25	9	9	18
26 to 30	14	9	23
31 to 35	19	12	31
36 to 40	32	17	49
41 to 45	56	23	79
Total	162	88	250

HYPERTENSION

That hypertension is followed by cardiac hypertrophy in the great majority of cases has been frequently observed. Paullin, Bowcock, and Wood,[9] in studying the complications of hypertension, found that cardiac hypertrophy occurred in 66.4 per cent of cases. In many cases of unexplained cardiac enlargement at the time of death, study of the records will show that a previous hypertension has existed. In 50 such cases O'Hare, Calhoun and Altnow [42] found that hypertension of varying grades had been present on earlier examinations, although during the terminal cardiac failure the pressure had dropped to normal.

The exact mechanism of cardiac hypertrophy is uncertain. That increased muscular work alone is insufficient to cause hypertrophy of the heart is shown by the fact that Marathon runners usually have hearts which are normal in size or even undersized.[7, 8] Eyster's [1, 4] demonstration of progressive cardiac hypertrophy in dogs after a temporary obstruction to blood flow in the aorta indicates that stretching of the muscle fibers may be the initial injury to which the fibers react by becoming hypertrophied. Whether this mechanism is operating in all cases of cardiac hypertrophy is uncertain, although it appears to be a rational explanation. The surprising absence of cardiac hypertrophy in some cases of prolonged hypertension may thus be explained by the supposition that the load was applied so gradually that dilatation never took place.

(*A*) *Hypertension with Nephritis.* The organic lesion elsewhere in the body with which abnormalities of the heart muscle were most often associated in the present series was chronic nephritis. Of the total of 250 cases, 67 or 26.8 per cent were found at autopsy to have one of the forms of

chronic nephritis.* The factor which was common to the great majority of the cases in this group was hypertension. Every case except one had a systolic blood pressure of 140 or more at the time of entry to the hospital; the one exception to this was a child of ten who had a blood pressure of 132/70, a distinct elevation for a child of that age. A systolic pressure of 200 or over was observed in 32 of the 67 cases, and a diastolic pressure of 100 or over was found in 57 cases. The heart weights in this group were all definitely above normal, the highest being 900 grams, and the average of the 65 adults (16 years and above) was 499.7 grams. Those with a systolic pressure of 200 or over had hearts averaging 537.6 grams. There is evidently some correlation between the degree of hypertension and the amount of hypertrophy, although other factors such as the duration of the hypertension, anemia, or intercurrent infections must also be considered.

Aside from hypertrophy there were very few changes in the gross appearance of the hearts in these cases. One showed small, flat yellowish areas in the epicardium and extending into the myocardium, while another had a few " milk patches " on the left ventricle and the right auricle. The microscopic appearance of the heart muscle was no more characteristic than the gross appearance. Thirty-one hearts were said to be normal microscopically, while 12 were not so examined. In the remaining 24 cases the microscopic changes varied from diffuse fibrosis to perivascular areas of fibrosis with or without cellular infiltration. In cases of malignant hypertension focal necroses were frequently described. Edema of the stroma, fragmentation of fibers, and increase in size of individual fibers were also noted.

Electrocardiograms were taken in but 22 of the cases and in 12 of these left axis deviation was noted. This agrees with the work of Ziskin [10] who found no constant changes in the electrocardiograms of 100 patients with hypertension, although 44 showed left axis deviation. Additional electrocardiographic changes in our group were inversion of the T-waves, low or high origin of the T-waves, and slurring of the QRS waves.

(*B*) *Hypertension without Nephritis.* Fourteen cases of hypertension in which the renal factor was negligible have been grouped under the heading, " Hypertensive Heart Disease without Nephritis."

Nothing beyond minor degrees of arteriosclerosis was found in the kidneys of the " purely hypertensive " cases. Since this form of heart disease is found largely in middle aged and elderly persons, it is not surprising that all our cases were in the upper range of our age group, between 38 and 45 years of age. In about half of the cases cardiac failure was the cause of death, while in the others cerebral hemorrhage or pulmonary embolism were the terminal events. The average weight of the hearts for this group was 545 grams. Grossly most of the hearts were hypertrophied and dilated, while microscopically generalized and patchy fibrosis was noted. The most

* Because of the necessity of condensing the article the tables of the individual cases have been omitted.

common electrocardiographic changes were left axis deviation and inversion of the T-waves.

(*C*) *Hypertension with Other Complications.* This rather heterogeneous group of 16 cases has been separated from the other sub-groups because a definite hypertension existed as a complicating factor. In six of the cases acute infections, which, as will be shown later, are sometimes accompanied by cardiac enlargement, were present in addition to the high blood pressure. The myocardium in these cases was normal except for minor grades of hypertrophy. Four cases showed extensive cardiac infarction as well as an elevated blood pressure. In addition to recent or healed infarction, the hearts exhibited marked hypertrophy with an average weight of 662.5 grams. Since both cardiac infarction and hypertension are capable of producing enlargement of the heart, the part played by each is impossible to estimate. In the other six cases, in addition to moderate elevation of blood pressure, the following diagnoses were recorded: pyonephrosis with uremia, chronic tubo-ovarian abscess, exophthalmic goiter, carcinoma of a bronchus with small metastatic nodules, lymphoblastoma, and cirrhosis of the liver. Myocardial changes, except for slight increase in weight, were insignificant except for the tumor nodules in the case of carcinoma of the bronchus and fatty infiltration in the last two cases mentioned above.

2. Acute and Chronic Infections

In 91 of the 250 selected cases acute and chronic infections were the primary causes of death. It is very difficult properly to evaluate the part played by the infectious process, since in many of the instances the marked cardiac enlargement indicated that another factor must have been at work. Those in which hypertension was known to have existed as a complicating factor have already been segregated into a separate group (1C). For purposes of discussion it is convenient to divide the cases in the following groups.

(*A*) *Acute Pulmonary Infections.* In all acute infections there is probably some toxic action on the heart, but in pneumonia there is the added factor of stasis in the pulmonary circuit and anoxemia. In 1915 Newburgh and Porter,[19] after injecting pneumonic blood into normal dogs, noticed that there was an initial loss of effectiveness of the heart as evidenced by a decreased stroke volume and lessened area of contraction. They observed, however, that this toxic effect wore off after a short while and that the heart rapidly readjusted itself to the altered conditions. So long as general nourishment was maintained and the initial dose was not too great the myocardium was quite able to cope with the toxin. In addition to this toxic effect, which in debilitated subjects may be quite marked, there is the added factor of increased resistance in the pulmonary circuit. Stone [20] found dilatation of the right heart in 39.4 per cent of 89 cases of lobar pneumonia and in 36.6 per cent of 112 cases of bronchopneumonia, while microscopi-

cally there was evidence of inflammatory and degenerative change in 61.9 per cent of 21 cases of lobar pneumonia and in 25 per cent of eight cases of bronchopneumonia. The whole heart was usually involved.

There were 32 cases of acute pleuro-pulmonary infections in our series, 23 of lobar pneumonia with and without complications, eight of bronchopneumonia with and without complicating conditions, and one of acute empyema. In all of these except one, the heart weight was above the average. The average weight of the hearts of the 28 adults was 413 grams.

In the majority of cases the myocardium was reported either as normal or as moderately hypertrophied or dilated. Microscopic examination was either essentially negative or not done in 23 of the cases, while in the others diffuse fibrosis was noted in four, cellular infiltration in two, fatty infiltration in one, and areas of necrosis and abscess formation in two. Four other cases of acute pulmonary infections were included under "Hypertension with Other Complications" because of a coincident high blood pressure.

(*B*) *Chronic Pulmonary Infections.* It has long been noted that chronic pulmonary disease, if obstruction to the pulmonary circulation is sufficiently great, results in a definite pulmonary hypertension with attendant strain on the right heart. Among the more common etiological agents are chronic bronchitis and emphysema, bronchiectasis, extensive fibrocaseous tuberculosis, thoracic deformities, extensive infiltrating tumors of the lungs, and endarteritis of the pulmonary vessels (Ayerza's disease). As Moschowitz [26] pointed out, obstruction to the pulmonary circulation by pressure upon or occlusion of the smaller vessels produces a hypertension which tends to engorge and dilate the right ventricle with eventual right sided hypertrophy. The added factor of pulmonary arteriosclerosis, which follows prolonged pulmonary hypertension, may serve eventually perhaps to aggravate the condition. When the right ventricle fails, the tricuspid ring is dilated and the effects are transmitted to the systemic venous circulation.

Long-continued bronchial asthma, especially when accompanied by emphysema, has sometimes been regarded as a cause of severe strain on the right heart, but recently Alexander and others,[24] in 50 such cases, were unable to find any evidence of myocardial damage as the result of asthma alone. Pulmonary abscess, unless extremely extensive, does not alter the mechanics of the lesser circulation, though it may exert a deleterious effect on the heart as a whole because of the toxemia. Tuberculosis, in addition to its pulmonary effects, may in rare instances involve the myocardium, producing lesions varying from disseminated miliary tubercles to large, caseous, tuberculous masses. Obliterating endarteritis of the pulmonary vessels (sometimes unsatisfactorily called Ayerza's disease) is a very rare condition which usually does not have a luetic origin. The pathological picture is that of an occluding endarteritis of the smaller pulmonary vessels with dilatation of the pulmonary artery and hypertrophy of the right heart. Cheney [25] considers it to be a distinct disease entity, while Moschowitz [26]

regards it, in the absence of proved etiology, as merely a syndrome which may be secondary to hypertension and sclerosis of the pulmonary circuit.

There were 17 cases of chronic pulmonary disease in our series in which definite cardiac changes were observed. Pulmonary abscess, bronchopneumonia, bronchiectasis, and pulmonary tuberculosis were the most frequent disorders, though there were two cases of emphysema, one case of silicosis and emphysema, and two cases of endarteritis obliterans.

Generalized enlargement of the heart was noted in five cases, left ventricular hypertrophy in one, and right ventricular hypertrophy in four, although in this last group the total heart weight was within normal limits in two. Microscopic changes were not particularly important or characteristic.

In one case of miliary tuberculosis a few miliary tubercles were found in a heart which was otherwise normal, while in another case of tuberculosis the incidental finding of a small rhabdomyoma was the only cardiac abnormality. The other changes reported were enlarged fibers in a case of right-sided hypertrophy, associated with bronchiectasis and emphysema, fatty infiltration in a case of tuberculosis and chronic alcoholism, small areas of scarring in a case in which a positive Kahn reaction and aortic changes brought up the question of cardiovascular syphilis, and an eosinophilia in a case of obliterating endarteritis. Electrocardiograms showed left axis deviation in the case of left ventricular hypertrophy and in one case of generalized enlargement and right axis deviation in a case of right ventricular hypertrophy. In three cases, other than the one noted above, the Kahn reaction was positive, although there was no evidence of cardiovascular syphilis.

(*C*) *Acute Infections Other than Pulmonary.* Acute infectious diseases in general cause no permanent injury to the heart muscle, though temporary functional derangement has been frequently observed. When there has been a concurrent intense toxemia, examination may show myocardial changes of a non-specific nature. Warthin [12] and others have described necrosis and hyaline degeneration of muscle fibers with the appearance of fatty changes and cloudy swelling in diphtheria; while Hamman [32] found fragmentation and swelling of the muscle fibers, interstitial edema, and perivascular fibrosis in severe typhoid fever. In other acute infections similar pictures have been reported, when death has occurred while toxemia has been intense. However, the lack of permanent injury is indicated by the return of normal function after the infection has subsided. White and Jones [31] were unable to find clinical evidence of cardiac damage in 100 cases five to eight years after severe diphtheria, while Brow,[28] in spite of Thayer's (quoted by Brow) assertion that elevated blood pressure and vascular sclerosis were frequent sequels of typhoid fever, found no indication of permanent ill effects in 65 cases of this disease one to 13 months after recovery. Rheumatic fever occupies a somewhat unique position among

acute infections, at least so far as cardiac involvement is concerned. Although endocardial damage is responsible for most of the late crippling effects, yet during the acute infection a pancarditis is almost the rule. After the acute disease is well established, the typical myocardial lesions are the Aschoff bodies, perivascular inflammatory reactions with round cell and giant cell infiltration. These lesions usually clear up after the acute infection has passed, although residual sclerosis has been reported.

That functional cardiac impairment does take place during the height of acute infectious disease is amply shown by electrocardiographic studies. Brow,[28] Burnett and Piltz,[17] and others have reported electrocardiographic changes in diphtheria, rheumatic fever, typhoid fever, pneumonia, influenza, and other acute infectious diseases. Prolongation of the P–R interval, slurring of the QRS complexes, and inversion of the T-waves are the usual findings and indicate disturbance of the conduction mechanism and myocardium. In diphtheria, particularly, conduction changes varying from simple prolongation of the P–R interval to complete A–V block as well as alterations in the T-waves are frequently noted. Except in rare instances it is the rule for these signs to disappear in a few months. There were 35 cases in our series showing myocardial damage or hypertrophy in acute infectious diseases.

In the five cases of diphtheria, the gross changes were not remarkable except for slight to moderate enlargement in three. Microscopically four of them showed hyaline degeneration with necrosis of fibers and cellular infiltration. The two cases of typhoid fever had essentially normal hearts except for moderate increase in weight. Three cases of scarlet fever were included because of the focal necroses and cellular infiltration of the myocardium. In one of them the lesions suggested Aschoff bodies. In two of them, one associated with acute nephritis and the other with pyelonephritis, there was definite cardiac enlargement when the age of the patient was taken into consideration. Of eight cases of meningitis due to the meningococcus or the streptococcus, the heart weight was above the normal in seven. Microscopic examination showed focal necroses in three of these. A case of encephalitis and bronchopneumonia showed occasional necrotic fibers and slight increase in heart weight. In the remaining 16 cases pyogenic infections were the immediate causes of death. The diagnoses included septicemia, pyemia, purulent arthritis, osteomyelitis, localized abscesses, and peritonitis. Definite increase in weight was noted in 11 and slight increase in three. In six cases microscopic examination showed no abnormalities and in two it was not done. In the remaining eight cases changes varied from focal fibrosis to necrosis and actual abscess formation. Abscess formation in the heart was found in cases of pyemia and formed a part of the general process.

Electrocardiograms were taken in four of the diphtheria cases. In three of them there was definite evidence of disturbance in the conduction

mechanism, while the fourth was normal. A tracing was made in one of the pyemic cases and was not remarkable except for left axis deviation.

No case of acute rheumatic infection is included in this series because in each case there was some associated valvular disease. Rare cases do exist of myocardial rheumatic involvement with little or no valvular disease, but none were found in the groups from which our series was drawn.

(*D*) *Chronic Infections Other than Pulmonary.* The effect of focal infections upon the heart is not very definitely understood. Bacterial endocarditis is infrequently associated with them, but no definite myocardial lesions have been found which may be related to focal infections. Aggravation of an existing heart disease or rarely minor arrhythmias may occur, but the relationship is far from certain.

There were seven cases of chronic non-pulmonary infectious disease with abnormalities of the heart without valvular deformities in our series. In five of them, the heart weight was definitely increased, in one the weight was borderline, and in one it was within normal limits. In three of the cases chronic infection of the kidneys undoubtedly produced some renal insufficiency, especially since in two cases only one kidney was functioning. In one case of luetic myelitis, the healed luetic aortitis and microscopic arterial changes may have accounted to some degree for the moderate increase in heart weight. Other microscopic changes were not remarkable except for the questionable Aschoff bodies in a case of a long-continued pyemic process with multiple septic joints.

3. Diseases of the Blood

Enlargement of the heart in severe anemias has been noted clinically by several observers and has been confirmed at necropsy. Gautier [37] reported demonstrable enlargement in 20 of 22 patients with severe chlorosis, while other writers have published series of cases of pernicious anemia in which this phenomenon was noted in from 30 per cent to 95 per cent. Goldstein and Boas [34] found extension of the heart borders by percussion in 23 of 39 cases of pernicious anemia, six of them verified by roentgen-ray. Twelve of this group which came to autopsy showed marked cardiac dilatation with gross weights varying from 250 to 460 grams, averaging 330 grams. "Tigering" of the myocardium was observed in six cases. That these changes are not peculiar to pernicious anemia but accompany any severe anemia is demonstrated by the observations of Goldstein and Boas,[34] Ball,[33] and others. Ball cited a case in which electrocardiographic changes characteristic of left ventricular preponderance practically disappeared with restoration of the normal blood level.

Anoxemia has been suggested as the cause of the dilatation and is probably the principal factor at work. There is undoubtedly some degree of hypertrophy in long-standing anemias, which may result from the cardiac dilatation. Fahr and Ronzone [35] reported an increase of as much as 250

per cent in the minute volume of the heart output, in one case of severe pernicious anemia. This compensatory mechanism is made possible by accelerated beat, increased stroke volume, and decreased viscosity of the blood.

In leukemias there is, in addition to the marked accompanying anemia, the weight of the infiltrating cells, which may in some cases be sufficient to produce an appreciable increase in heart weight.

There were 27 cases of blood dyscrasias in our series: acute and chronic leukemia 17; aplastic anemia 3; hemolytic jaundice 2; pernicious anemia 1; purpura hemorrhagica 1; sickle cell anemia 1; agranulocytosis 1; and erythroblastosis neonatorum 1.

There were 17 cases of acute and chronic leukemia in this group. Among the adults with leukemia the heart weights varied between 200 and 498 grams with but six of the number above the normal limits. There did not seem to be any correlation between heart weight and the duration of the disease or the predominant type of cell. In the three children (cases 3, 6, and 13) the hearts were considerably heavier than one would expect at their ages. In almost all the 17 cases there was marked anemia, which in itself may cause dilatation and some hypertrophy of the heart. Grossly the hearts were described as pale, lax, flabby, and sometimes dilated, while microscopically there was considerable infiltration with leukemic cells in most cases, attaining in places the proportion of an actual tumor growth. Petechial hemorrhages were a fairly common finding. Among the other 10 cases of blood diseases five showed definite increase in heart weight. Dilatation, hypertrophy, petechial hemorrhages, and mottling of the myocardium were noted grossly, while microscopically, in those cases in which abnormalities occurred, diffuse fibrosis, petechial hemorrhages, and vacuolization of fibers were described. This last condition was found in three cases: one of aplastic anemia, one of sickle cell anemia, and one of erythroblastosis neonatorum. In the first two there was marked anemia, while in the last case death occurred so quickly that blood studies were not carried out. In a case of arsphenamine agranulocytosis, the cardiac enlargement was very striking, when the age is considered, although the anemia was not pronounced. Only one case of pernicious anemia was found in the series, probably because of the introduction of liver therapy during the past decade.

4. Coronary Occlusion

The immediate effects of occlusion of a large branch of the coronary arteries may be extreme dilatation and failure of the heart. The part supplied by the occluded vessel becomes infarcted, and if the patient survives, the whole area eventually becomes fibrotic. The early dilatation to a large degree disappears, but if the infarcted area is large, hypertrophy of varying degrees takes place. Recently Smith and Bartels [40] cited two cases of extensive coronary occlusion in which the heart weights were greatly

increased; there was enormous dilatation without much increase in thickness of the ventricular walls. These authors followed this report with a much larger series of 42 cases [41] of coronary occlusion from which all other possibilities of hypertrophy had been eliminated. They calculated the normal heart weights by Smith's method and found a definite increase in weight of from 9 per cent to 108 per cent in 37 of the 42 cases, the actual weights varying between 265 and 715 grams. The average increase in weight above the calculated normal for the whole group was 44 per cent. From this study they concluded that coronary occlusion with cardiac infarction was a definite cause of hypertrophy.

There were five cases of coronary occlusion in our series in which there was neither history nor evidence of hypertension at the time of admission to the hospital. In addition there were four other cases of coronary occlusion with definite hypertension which were included under the heading "Hypertension with Other Complications."

Although all these hearts were very definitely above the normal weight (average 518 grams), it is difficult to draw conclusions from so small a group. A previous hypertension is almost impossible to exclude, since some of the patients were in a condition of shock on entering the hospital. The myocardial changes consisted of hypertrophy and of old or recent infarcts. The electrocardiographic changes, left axis deviation, bundle branch block, and altered QRS and T-waves are consistent with recent and old coronary occlusion and with hypertension.

5. Congenital Hypertrophy of the Heart

According to Kugel and Stoloff [44] only 52 cases of congenital idiopathic hypertrophy of the heart had been reported up to 1933, in addition to the seven which they reported in April of that year. These authors consider that only those cases which show pure hypertrophy of the muscle fibers should be considered as idiopathic hypertrophy, and that if such changes as fibrosis or any kind of degeneration are present, the heart cannot then be said to be an example of idiopathic hypertrophy. Using this standard they found that only 17 out of 59 cases had "true idiopathic hypertrophy," the remaining cases showing changes secondary to some other process.

Many different causes for congenital hypertrophy of the heart have been suggested, but no one has been found to be operative in a considerable number of individuals. In one of our cases, which has already been reported,[45] glycogen storage (von Gierke's) disease was later found responsible, and there was a very unusual family history in that several members of the family had cardiac defects, thus suggesting the probability of an inheritance of a tendency to this cardiac anomaly. Bland, White, and Garland [48] have recently reported the case of a male infant dying at the age of three months, in whom at autopsy the left coronary artery arose from the pulmonary artery and the enlarged heart showed much disease of the left

ventricular myocardium; eight similar cases had been previously reported. Other possible etiological factors which have been mentioned as causes of cardiac hypertrophy in infancy besides congenital septal and valvular defects are infection, hypertension in the parents, enlarged thymus, and congenital medial sclerosis.

There were four cases of congenital hypertrophy in our series. In the first three this diagnosis was made clinically, while in the last the case was regarded as one of cardiac hypertrophy of unknown origin in an infant.

In our four cases the weight of the hearts was increased from two to six times the normal. Two of the hearts were described as dilated, one as enlarged, and one as enlarged with right ventricular hypertrophy and petechial hemorrhages over the left ventricular base. Microscopic changes were unimportant except for hypertrophied and vacuolated fibers in one of the cases. One case died of congestive failure, one of congestive failure and bronchopneumonia, one at birth, while the immediate cause of death in the fourth was uncertain.

6. Hyperthyroidism

There has always been a division of opinion as to whether hyperthyroidism per se produces definite myocardial abnormalities, or whether the cardiac pathological changes are the result of increased metabolism. Recently Rake and McEachern [54] examined the hearts of 27 autopsied cases of hyperthyroidism, and, by comparing the results with those from supposedly normal hearts of similar age groups, found only five of the 27 with changes more marked than in the controls. Muscular scarring, perivascular fibrosis, cellular infiltration, and altered staining reactions were reported in the five cases noted above, with lesser degrees of the same findings in many others. The writers considered the picture to be merely an accentuation of normal katabolic changes brought on by the increased metabolic and cardiac activity and in no way peculiar to the hyperthyroid state. Kepler [50] studied 57 cases of exophthalmic goiter and 16 cases of toxic adenoma from the point of view of hypertrophy of the heart and found that 49 per cent of them showed an increase in weight when compared with the Smith standards. The body weights used in the calculations were those prior to the onset of the condition. Burnett and Durbin [52] found evidence of definitely abnormal axis deviation in 24 of 62 patients: right in 7, and left in 17.

There were nine cases with the clinical diagnosis of hyperthyroidism which came to autopsy over this period. In seven of them the heart was described as normal. In the other two, one of them complicated by a moderate hypertension, the heart weight was moderately increased, though the myocardium was apparently normal. The "bile staining," noted in one of them, was a part of a general icterus, while the rather high systolic pressure was probably secondary to the thyrotoxicosis rather than of the essential variety.

7. Cardiac Failure of Uncertain Etiology

A few years ago Christian [38] pointed out that there are a large number of cases of cardiac failure occurring in middle age for which there is no obvious reason. He stated that although arteriosclerosis, coronary disease, previous acute infections, or previous hypertension may account for some, yet in many no etiological agent is apparent. Clinically there is evidence of muscular deficiency, but physical examination and electrocardiographic studies may be entirely negative. Pathologically the hearts are often hypertrophied and may or may not show fibrosis.

There were eight cases in our series which seemed to fall into this group. In three of them there was a strong possibility of a previous hypertension, although the pressures recorded did not justify inclusion in that group.

Of these cases all except two were in the very upper limits of our age group. Cardiac enlargement, in two cases of marked degree, was noted in six instances. Failure to record the blood pressure in three cases naturally makes exclusion of hypertension impossible, while a marked anemia in another may well have been an etiological factor. Myocardial changes consisted of dilatation, hypertrophy, and gross and microscopic scarring. Electrocardiograms gave evidence of disturbed conduction, either in the bundle or in the ventricular muscle.

One of the cases (case 8 in the tables) is of particular interest because of the youth of the patient. On his first entry to the hospital he presented the picture of cardiac decompensation which was considered to be probably on a rheumatic basis, although no specific history was obtained. After a few weeks in the ward he was discharged greatly improved to a convalescent home where he remained off and on for eight months. At that time his symptoms returned and he reëntered the hospital where he died in a short time. Autopsy did not explain the cause of his cardiac failure. Somewhat similar cases of idiopathic cardiac hypertrophy have recently been reported by Levy.[43]

8. Miscellaneous

Seventeen cases were of so varied a nature that they have been placed in a miscellaneous group. The diagnoses in this group include: generalized malignancy 5, brain tumor 3, cirrhosis of the liver 2, rhabdomyoma 1, ruptured aortic aneurysm 1, gastric ulcer with hemorrhage 1, thrombosis of portal vein 1, nephrosis 1, enlargement of liver and spleen of unknown cause 1, and pregnancy and labor 1.

Of the five cases of generalized malignancy, four showed definite increase in heart weight with metastatic involvement of the myocardium in two. Cardiac enlargement was observed in all three cases of intracranial tumor and in one of them there was malignant involvement of the heart muscle. The largest heart in this group was associated with cirrhosis of the liver and luetic aortitis; it was impossible to tell if either factor was really connected with the hypertrophy. In the case of uncomplicated cir-

rhosis the enlargement was not so striking. In the remaining seven cases increase in heart weight was noted in six, and, with the exception of two cases, for no very obvious reason. In one case the myocardium was riddled with a rhabdomyoma, nodules of which partly occluded two valves, while in another, a 6 year old boy, degenerative changes in the myocardium were found with general glandular enlargement of unknown etiology. In the one case of nephrosis (case 15) the weight was well within normal limits, but atrophy and fatty infiltration of the myocardium were reported.

Although it is impossible to draw any conclusions from so varied a group, yet the frequent association of cardiac hypertrophy with malignancy is difficult to explain, except where metastatic involvement occurred. There was no marked degree of anemia in any of these cases, nor was there any other apparent cause of enlargement.

Summary

An analysis has been made by us of 250 instances of myocardial abnormality in individuals under the age of 46 years without valvular disease or congenital defects found among 4,531 cases examined post mortem at the Massachusetts General and Boston City Hospitals.

There were 97 cases with hypertension in which the chief cardiac lesion was hypertrophy with diffuse or perivascular fibrosis in about 40 per cent.

There were 91 cases of acute and chronic infections in which cardiac abnormalities were observed. In acute pulmonary infections hypertrophy of the heart was frequently noted with dilatation, edema of the muscle, and occasionally focal necroses. In the chronic pulmonary infections generalized or right ventricular enlargement was noted in several cases without characteristic microscopic changes. In acute infections other than pulmonary, there occurred severe muscle damage in diphtheria, focal necroses frequently in severe toxemias, and occasional miliary abscesses in extensive pyemias. In chronic infections other than pulmonary there was often moderate increase in heart weight with myocardial fibrosis in some cases.

There were 27 cases of various blood dyscrasias in which hypertrophy was noted in less than half, with microscopic changes consisting of fatty infiltration, slight fibrosis, petechial hemorrhages, and leukemic infiltration.

Nine cases of coronary thrombosis, five complicated by known hypertension, showed marked hypertrophy with recent or old infarction.

In four cases of congenital cardiac hypertrophy in infants, there was marked increase in heart weight with negligible microscopic changes except for hypertrophy and vacuolization of muscle fibers in one case.

In two cases of hyperthyroidism, one complicated by systolic hypertension, there was moderate cardiac enlargement without significant microscopic changes.

In eight cases of cardiac failure of uncertain etiology, hypertrophy and myocardial fibrosis were the most important lesions.

In seventeen miscellaneous cases no constant changes were observed, though the association of myocardial abnormalities with generalized and intracranial malignancy in several cases was interesting.

We wish to express our thanks to Dr. Paul D. White for his never-failing aid in the assembling and critical analysis of our material. It was at his suggestion that this study was begun and it was through him that it finally reached its present form. We wish also to acknowledge the courtesy and coöperation of the Pathological Departments of the Massachusetts General and Boston City Hospitals in granting permission to use their material.

BIBLIOGRAPHY

Dilatation and Hypertrophy of the Heart

1. Eyster, J. A. E.: Cardiac dilatation and hypertrophy, Trans. Assoc. Am. Phys., 1927, xlii, 15.
2. Smith, H. L.: The relation of the weight of the heart to the weight of the body and the weight of the heart to age, Am. Heart Jr., 1928, iv, 79.
3. Bell, E. T., and Hartzell, T. B.: Studies on hypertension. The relation of age to the size of the heart, Jr. Med. Research, 1924, xliv, 473.
4. Eyster, J. A. E.: Experimental and clinical studies in cardiac hypertrophy, Jr. Am. Med. Assoc., 1928, xci, 1881.
5. Stewart, H. J.: The effect of exercise on the size of normal hearts and of enlarged hearts of dogs, Jr. Clin. Invest., 1924, vii, 339.
6. Vierordt, K. H.: Anatomische, physiologische, und physicalische Daten und Tabellen zum Gebrauche für Mediziner, 3d edition, 1906, Gustav Fischer, Jena.
7. Gordon, B., Levine, S. A., and Wilmaers, A.: Observations on a group of Marathon runners with special reference to the circulation, Arch. Int. Med., 1924, xxxiii, 425.
8. Bramwell, C., and Ellis, R.: Some observations on the circulatory mechanism in Marathon runners, Quart. Jr. Med., 1931, xxiv, 329.

The Heart in Hypertension and Nephritis

9. Paullin, J. E., Bowcock, H. M., and Wood, R. H.: Complications of hypertension, Am. Heart Jr., 1927, ii, 613.
10. Ziskin, T.: The electrocardiogram in hypertension, Arch. Int. Med., 1928, xlii, 512.
11. Cabot, R. C.: Facts on the heart, 1926, W. B. Saunders and Co., Philadelphia, page 444.

The Heart in Acute and Chronic Infections

12. Warthin, A. S.: The myocardial lesions in diphtheria, Jr. Infect. Dis., 1924, xxxv, 32.
13. Swift, H. F.: The heart in infection, Am. Heart Jr., 1928, iii, 629.
14. Levy, R. L.: The size of the heart in pneumonia, Arch. Int. Med., 1923, xxxii, 359.
15. Scarlett, E. P.: The significance of infection in cardiovascular disease, Canad. Med. Assoc. Jr., 1932, xxvi, 562.
16. Ritchie, W. T.: Treatment of circulatory failure, Glasgow Med. Jr., 1931, cxv, 161; *Abstract* Acute circulatory failure, Lancet, 1931, i, 190.
17. Burnett, C. T., and Piltz, G. F.: The electrocardiogram in the acute infections, Jr. Am. Med. Assoc., 1929, xciii, 1120.
18. White, P. D.: The heart in infectious disease, Am. Jr. Med. Sci., 1922, clxiii, 335.
19. Newburgh, L. H., and Porter, W. T.: The heart muscle in pneumonia, Jr. Exper. Med., 1915, xxii, 123.
20. Stone, W. J.: The heart muscle changes in pneumonia, with remarks on digitalis therapy, Am. Jr. Med. Sci., 1922, clxiii, 659.
21. Hamburger, W. W., and Priest, W. S., Jr.: Structural and functional involvement of the heart following acute respiratory and other acute infections, Am. Jr. Med. Sci., 1923, clxvi, 629.

22. Rose, E.: Typhoid infection with mitral stenosis, Med. Clin. N. Am., 1930, xiii, 969.
23. Maher, C. C.: Heart disease and pulmonary pathology, Med. Clin. N. Am., 1931, xv, 737.
24. Alexander, H. L., Luten, D., and Kountz, W. B.: The effects on the heart of long-standing bronchial asthma, Jr. Am. Med. Assoc., 1927, lxxxviii, 882.
25. Cheney, G.: Ayerza's disease, with a report of two cases, Am. Jr. Med. Sci., 1927, clxxiv, 34.
26. Moschowitz, E.: Hypertension of the pulmonary circulation: its causes, dynamics, and relation to other circulatory states, Am. Jr. Med. Sci., 1927, clxxiv, 388.
27. White, P. D.: The relationship of the heart and lungs in disease, Arch. Surg., 1929, viii, 339.
28. Brow, G. R.: The heart in typhoid fever, Canad. Med. Assoc. Jr., 1929, xx, 606.
29. Weiss, E.: Tuberculosis of the heart with a report of two cases, Arch. Int. Med., 1922, xxix, 64.
30. Anders, J. M.: Tuberculosis of the myocardium, Jr. Am. Med. Assoc., 1902, xxxix, 1081.
31. White, P. D., and Jones, T. D.: The heart after severe diphtheria, Am. Heart Jr., 1927, iii, 190.
32. Hamman, L.: The heart muscle in typhoid fever, Arch. Int. Med., 1910, vi, 339.

The Heart in Diseases of the Blood

33. Ball, D.: Changes in the size of the heart in severe anemias with report of a case, Am. Heart Jr., 1931, vi, 517.
34. Goldstein, B., and Boas, E. P.: Functional diastolic murmurs with cardiac enlargement in severe anemia, Arch. Int. Med., 1927, xxxix, 226.
35. Fahr, G., and Ronzone, E.: Circulatory compensation for deficient oxygen carrying capacity of the blood in severe anemias, Arch. Int. Med., 1922, xxix, 331.
36. Gwyn, N. B.: Angina pectoris occurring in the course of certain anemias, Canad. Med. Assoc. Jr., 1932, xxvi, 26.
37. Gautier, E.: Über die morphologischen Veränderungen des Herzen bei der Chlorose auf Grund klinischer Beobachtungen, Deutsch. Arch. f. klin. Med., 1889, lxii, 120.

Myocarditis and Coronary Occlusion

38. Christian, H. A.: Chronic non-valvular disease of the heart, Jr. Am. Med. Assoc., 1928, xci, 549.
39. Hyman, A. S., and Parsonnet, A. E.: Myocardosis—the failing heart of middle life. II. Early clinical manifestations, New England Jr. Med., 1931, cciv, 648.
40. Smith, H. L., and Bartels, E. C.: Coronary thrombosis with myocardial infarction and hypertrophy in young persons. A report of two cases with necropsy, Jr. Am. Med. Assoc., 1932, xcviii, 1072.
41. Bartels, E. C., and Smith, H. L.: Gross cardiac hypertrophy in cardiac infarction, Am. Jr. Med. Sci., 1932, clxxxiv, 452.
42. O'Hare, J. P., Calhoun, A. W., and Altnow, H. O.: Etiology of chronic myocarditis, Jr. Am. Med. Assoc., 1928, xc, 1436.
43. Levy, R. L.: Cardiac hypertrophy of unknown etiology in young adults, Trans. Assoc. Am. Phys., 1933, lxviii, 125.

Congenital Idiopathic Hypertrophy

44. Kugel, M. A., and Stoloff, E. G.: Dilatation and hypertrophy of the heart in infants and in young children, Am. Jr. Dis. Child., 1933, xlv, 828.
45. Sprague, H. B., Bland, E. F., and White, P. D.: Congenital idiopathic hypertrophy of the heart, Am. Jr. Dis. Child., 1931, xli, 877.
46. Carrington, G. L., and Krumbhaar, E. B.: So-called idiopathic cardiac hypertrophy in infancy, Am. Jr. Dis. Child., 1924, xxvii, 449.

47. KISSANE, R. W., and FIDLER, R. S.: Congenital medial sclerosis of the coronary arteries, Am. Heart Jr., 1931, vii, 133.
48. BLAND, E. F., WHITE, P. D., and GARLAND, J.: Congenital anomalies of the coronary arteries. Report of an unusual case associated with cardiac hypertrophy, Am. Heart Jr., 1933, viii, 787.
49. STOLOFF, E. G.: So-called idiopathic enlargement of the heart in infancy and childhood, Am. Jr. Dis. Child., 1928, xxxvi, 1204.

The Heart in Hyperthyroidism

50. KEPLER, E. J.: Hypertrophy of the heart with congestive failure in hyperthyroidism: a clinical and pathological study of 178 cases, Proc. Staff Meet. Mayo Clin., 1932, vii, 397.
51. WELLER, C. V., WANSTROM, R. C., GORDON, H., and BUGHER, J. C.: Cardiac histopathology in thyroid disease; preliminary report, Am. Heart Jr., 1932, viii, 8.
52. BURNETT, C. T., and DURBIN, E.: Signs and symptoms of heart changes in toxic goiter, Am. Heart Jr., 1932, viii, 29.
53. FAHR, G.: Myxedema heart. A report based upon the study of 17 cases, Am. Heart Jr., 1932, viii, 91.
54. RAKE, G., and MCEACHERN, D.: A study of the heart in hyperthyroidism, Am. Heart Jr., 1932, viii, 19.

THE SIGNIFICANCE OF SPECIFIC PNEUMOCOCCUS TYPES IN DISEASE, INCLUDING TYPES IV TO XXXII (COOPER) *

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THE recent increase in the use of specific serum for the treatment of pneumonia has been accompanied by a growing interest in the newer types of pneumococci [1] in many parts of this and other countries. It seems appropriate, therefore, to present a brief résumé of 3682 cases admitted to the Boston City Hospital, from which pneumococci were cultured and typed with the aid of serums for these new types. Approximately one-third of these cases, previously reported,[2] occurred before June 1, 1932 and were typed with serums for Types I to XX. The remaining cases were admitted before July 1, 1936 and were typed with serums for Types I to XXXII, inclusive.

PATIENTS, SOURCES OF PNEUMOCOCCI, AND METHODS

These are described in previous papers [3] in which selected groups of cases were analyzed in considerable detail. The serums used in the classification of pneumococci Types IV to XXXII were obtained through the generosity of Dr. William H. Park and the late Miss Georgia Cooper of the Bureau of Laboratories of the New York City Department of Health. The bacteriologic and pathologic data were made available through the kindness of Dr. Frederick Parker, Jr. and Dr. Robert N. Nye of the Mallory Institute of Pathology of the Boston City Hospital. To them, to the resident and visiting staffs of the Boston City Hospital, and to the physicians and laboratory assistants who, at different times, participated directly in this study, the author acknowledges his gratitude.

ANNUAL AND MONTHLY INCIDENCE OF THE VARIOUS PNEUMOCOCCUS TYPES

The total number of cases of pneumococcic infections varied considerably from year to year (table 1).† The annual incidence of some of the individual pneumococcus types fluctuated even more widely. Noteworthy is the sharp increase in the number of cases of infection with Types II, V and VII pneumococci during the 1935 to 1936 season. The mortality also varied in different seasons.[3c, d]

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† In the tables, the Types XXVI and XXX have been omitted. The former is probably identical with Type VI and the latter is either closely related to or identical with Type XV. Type XXX was identified in two cases, one with lobar pneumonia, the other with a common cold; these are included with the Type XV cases.

TABLE I

Annual Incidence of Infections with the Various Types of Pneumococci
(Boston City Hospital, November 1929 to June 1936)

Type	1929–1930	1930–1931	1931–1932	1932–1933	1933–1934	1934–1935	1935–1936	Totals
I	117	109	81	112	153	141	160	873
II	51	60	55	54	25	18	90	353
III	57	69	65	91	101	88	101	572
IV	4	5	11	15	12	23	15	85
V	13	20	17	55	32	26	105	268
VI	3	2	18	21	20	19	14	97
VII	14	24	20	20	28	22	67	195
VIII	19	16	40	50	33	72	49	279
IX	2	9	6	11	8	6	14	56
X	1	22	13	16	11	23	16	102
XI	0	13	9	5	6	13	21	67
XII	2	6	3	9	7	18	12	57
XIII	1	1	5	8	5	4	9	33
XIV	0	9	11	15	26	14	30	105
XV	2	2	2	3	3	4	2	18
XVI	0	0	2	2	2	6	2	14
XVII	0	0	9	6	6	11	17	49
XVIII	16	7	12	10	12	18	20	95
XIX	—	1	7	10	10	12	7	47
XX	—	—	17	16	22	15	23	93
XXI	—	—	0	1	4	9	12	26
XXII	—	—	1	6	2	11	6	26
XXIII	—	—	—	0	1	2	7	10
XXIV	—	—	—	3	0	4	1	8
XXV	—	—	—	2	0	0	5	7
XXVII	—	—	—	0	0	1	1	2
XXVIII	—	—	—	0	0	3	3	6
XXIX	—	—	—	1	1	4	7	13
XXXI	—	—	—	1	0	4	0	5
XXXII	—	—	—	0	0	1	4	5
Neg. I–XX	44	36	28	3	—	—	—	111
Neg. I–XXXII	—	—	3	0	0	0	2	5
TOTAL	346	411	435	546	530	592	822	3682

The month of greatest incidence of all pneumococcic infections was always one of the winter months (January to March), but it varied in different years. While the peak of incidence was usually the same for most of the common types, disproportionate increases occurred at various times for individual types.[3b]

OCCURRENCE OF SPECIFIC PNEUMOCOCCUS TYPES IN DIFFERENT DISEASES

All of the cases with typed pneumococci were divided into six groups and the number and percentage of cases of each type occurring within each category are given in table 2. All patients over 12 years of age are listed as adults. The groups may be described briefly:

A. Under *lobar pneumonia* are included all cases with uniform consolidation in one or more lobes of the lung according to the best evidence obtainable from pathological, roentgenological, or physical examination. In

table 2, the cases in which there was additional patchy or atypical solidification in other parts of the lung were included in this category. The most frequent types in this group were Types I, III, II, V, VIII, and VII, in the order named. These six types together accounted for 79 per cent of the cases of lobar pneumonia.

TABLE II

Occurrence of Pneumococcus Types in Disease

Type	*A.* Lobar Pneumonia in Adults *		*B.* Atypical Pneumonia in Adults		*C.* Empyema on Admission in Adults		*D.* Pneumonia and/or Empyema in Children		*E.* Focal Infections (No Pneumonia)		*F.* Carriers and Respiratory Infections without Pneumonia		All Cases	
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
I	654	29.3	28	4.5	27	39	118	55.1	34	14.0	12	3.9	873	23.7
II	294	13.2	15	2.4	10	15	9	4.2	17	7.0	8	2.6	353	9.6
III	335	15.0	99	16.0	5	7	6	2.8	76	31.3	51	16.6	572	15.5
IV	46	2.1	18	2.9	1	1	4	1.9	6	2.5	10	3.2	85	2.3
V	191	8.6	30	4.8	5	7	19	8.9	17	7.0	6	1.9	268	7.3
VI	28	1.3	30	4.8	3	4	8	3.7	10	4.1	18	5.8	97	2.6
VII	128	5.7	32	5.2	4	6	2	0.9	10	4.1	19	6.2	195	5.3
VIII	159	7.2	68	11.0	8	12	4	1.9	22	9.1	18	5.8	279	7.6
IX	30	1.3	12	1.9	2	3	3	1.4	2	0.8	7	2.3	56	1.5
X	37	1.7	40	6.5	1	1	2	0.9	5	2.1	17	5.5	102	2.8
XI	29	1.3	18	2.9	0	0	4	1.9	8	3.3	8	2.6	67	1.8
XII	38	1.7	8	1.3	1	1	4	1.9	3	1.2	3	1.0	57	1.5
XIII	13	0.6	12	1.9	0	0	0	0	2	0.8	6	1.9	33	0.9
XIV	51	2.3	24	3.9	1	1	15	7.0	7	2.9	7	2.3	105	2.9
XV	7	0.3	6	1.0	0	0	0	0	0	0	5	1.6	18	0.5
XVI	4	0.2	8	1.3	0	0	1	0.5	0	0	1	0.3	14	0.4
XVII	19	0.9	20	3.2	0	0	2	0.9	1	0.4	7	2.3	49	1.3
XVIII	38	1.7	32	5.2	0	0	1	0.5	4	1.6	20	6.5	95	2.6
XIX	19	0.9	12	1.9	0	0	4	1.9	5	2.1	7	2.3	47	1.3
XX	36	1.6	35	5.7	0	0	4	1.9	3	1.2	15	4.9	93	2.5
XXI	9	0.4	9	1.5	0	0	1	0.5	3	1.2	4	1.3	26	0.7
XXII	10	0.4	10	1.6	0	0	0	0	2	0.8	4	1.3	26	0.7
XXIII	2	0.1	3	0.5	0	0	1	0.5	0	0	4	1.3	10	0.3
XXIV	0	0	3	0.5	0	0	0	0	0	0	5	1.6	8	0.2
XXV	3	0.1	2	0.3	0	0	0	0	1	0.4	1	0.3	7	0.2
XXVII	1	0	0	0	0	0	0	0	0	0	1	0.3	2	0.1
XXVIII	0	0	4	0.6	0	0	0	0	1	0.4	1	0.3	6	0.2
XXIX	4	0.2	4	0.6	0	0	0	0	2	0.8	3	1.0	13	0.4
XXXI	3	0.1	0	0	0	0	0	0	0	0	2	0.6	5	0.1
XXXII	3	0.1	1	0.2	0	0	0	0	0	0	1	0.3	5	0.1
Neg. I–XX †	35	1.6	35	5.7	1	1	1	0.5	2	0.8	37	12.0	111	3.0
Neg. I–XXXII	3	0.1	1	0.2	0	0	1	0.5	0	0	0	0	5	0.1
TOTALS	2229	100	619	100	69	100	214	100	243	100	308	100	3682	100

* Includes cases with lobar pneumonia in one or more lobes and atypical in other parts.

† Some of the cases previously included (2) have been omitted because of insufficient data to classify the organisms as pneumococci.

B. All cases with patchy or with peribronchial pulmonary consolidation were included as *atypical pneumonia,*[4] a designation used throughout this paper instead of the term "bronchopneumonia." The most frequent types in these cases were Types III, VIII, X, XX, XVIII, and VIII which, together, accounted for one-half the cases of this group.

The pneumococcus types in the cases of pneumonia in adults (groups *A* and *B*) were obtained from cultures of either sputum, blood, lung, infected exudates or autopsy material, or from more than one of these sources. In about half the cases the sputum was the only source.

C. Cases of *adults with empyema* present at the time of admission, in which the pneumococcus type was obtained from the infected pleural exudate, are listed separately. The types most frequent in this group were the same, except for order, as among the cases of lobar pneumonia in adults, namely Types I, II, VIII, III, V, and VII, which accounted for 84 per cent of the group.

D. Most of the cases of *pneumonia in children,* with or without empyema, were typed either from pleural exudate or from material obtained at autopsy. In occasional cases, the pneumococci were obtained from blood cultures or, more rarely, from sputum or throat cultures. About two-thirds of these cases had empyema. Type I alone accounted for more than half of the cases. Types V, XIV, II, VI and III, respectively, ranked next in frequency. These six types included 82 per cent of the cases of this group.

E. Under *focal infections* are included cases in all age groups in which the pneumococci were cultured from the infected focus and in which there was no evidence of pneumonia at the time. Type III organisms were most frequent in this group, with Types I, VIII, II, and V following in the order named. Together, these five types included slightly more than one-half the cases in this category.

F. The last group includes cases of *acute or chronic respiratory infections* where there was no evidence of pneumonia attributable to the pneumococcus. This group also includes cases that may be termed *carriers,* in whom the pneumococci were obtained from routine nasal, pharyngeal, or sputum cultures taken during the course of other diseases and in whom there was no evidence of infection attributable to the pneumococcus. In this group, Types III, XVIII, VII, VI, VIII, X, and XX were most common, in that order, these seven types constituting more than half of the total.

Cases with Autopsy

In 764 of the fatal cases there was an opportunity to ascertain at necropsy the relationship of the pneumococcus to the infection. The classification of the autopsied cases according to the pneumococcus type, with particular reference to the character of the pulmonary lesion in the cases with pneumonia, is given in table 3. The six most frequent types in the cases with lobar pneumonia were the same, in essentially the same order, as noted in

table 2, namely, Types I, III, II, V, VII, and VIII, these types accounting for 83 per cent of the cases. One-sixth of all the cases that had lobar pneumonia at autopsy also showed some areas of atypical consolidation in other portions of the lung.

TABLE III

Occurrence of Pneumococcus Types in Autopsied Cases

Type	Lobar Pneumonia		Atypical Pneumonia		Mixed: Lobar and Atypical Pneumonia	Focal Infection without Pneumonia	No Proved Relation to Disease	Total	
	Number	Per cent	Number	Per cent	Number	Number	Number	Number	Per cent
I	104	30.7	21	7.2	13	5	2	145	19.0
II	43	12.7	11	3.8	2	8	1	65	8.5
III	81	23.9	47	16.2	11	17	4	160	20.9
IV	14	4.1	9	3.1	2	2	2	29	3.9
V	32	9.4	22	7.6	7	5	0	66	8.6
VI	5	1.5	15	5.2	0	1	1	22	2.9
VII	17	5.0	16	5.5	5	3	0	41	5.4
VIII	17	5.0	28	9.7	3	5	2	55	7.2
IX	4	1.2	6	2.1	0	1	1	12	1.6
X	4	1.2	19	6.6	2	1	0	26	3.4
XI	1	0.3	8	2.8	0	4	0	13	1.7
XII	3	0.9	9	3.1	1	1	0	114	1.8
XIII	1	0.3	4	1.4	0	0	0	5	0.7
XIV	6	1.8	8	2.8	5	0	0	19	2.5
XV	0	0	0	0	0	0	1	1	0.1
XVI	0	0	6	2.1	0	0	0	6	0.8
XVII	0	0	7	2.4	1	0	0	8	1.0
XVIII	4	1.2	12	4.1	1	1	1	19	2.5
XIX	1	0.3	3	1.0	1	1	0	6	0.8
XX	0	0	14	4.8	1	1	0	16	2.1
XXI	1	0.3	2	0.7	0	1	0	4	0.5
XXII	1	0.3	5	1.7	0	1	1	8	1.0
XXIII	0	0	3	1.0	0	0	0	3	0.4
XXIV	0	0	1	0.3	0	0	0	1	0.1
XXV	0	0	0	0	0	1	0	1	0.1
XXVII	0	0	1	0.3	0	0	0	1	0.1
XXVIII	0	0	1	0.3	0	1	0	2	0.3
XXIX	0	0	2	0.7	0	1	1	4	0.5
Neg. I–XX	0	0	10	3.4	0	1	1	12	1.6
TOTALS	339	100	290	100	55	62	18	764	100

Among the cases in which only atypical pneumonia was found in the lungs at autopsy, Types I and V ranked high in incidence, in addition to the types noted previously for the entire group. The most common types among these cases, in the order of their frequency were: Types III, VIII, V, I, X, VI, VII, XX, and XVIII, these nine types including 68 per cent of the total. The discrepancy between the relative frequency in the entire group and in the autopsied cases is explicable on the basis of differences in mortality rates, as will be noted below.

TABLE IV

Focal Purulent Infections with the Various Types of Pneumococci

Pneumococcus Type	Cases without Pneumonia				Cases Complicating Pneumonia † (adults)							
	Otitis Media and/or Mastoiditis	Meningitis	Peritonitis	Others *	Empyema	Pericarditis	Lung Abscess	Endocarditis	Meningitis	Otitis Media	Peritonitis	Subcutaneous Abscesses
I	10	4	5	14	93	13	16	5	2	11	2	12
II	4	4	2	7	18	4	10	6	6	5	0	6
III	37	15	9	15	37	19	28	2	3	6	3	4
IV	1	4	0	1	4	0	1	0	1	1	0	0
V	9	3	3	2	31	6	8	3	3	6	6	4
VI	2	2	3	3	3	5	4	1	0	0	0	0
VII	4	4	1	1	9	5	1	3	3	2	0	1
VIII	1	4	7	11	15	1	5	2	8	1	1	2
IX	0	2	0	0	4	0	2	0	0	0	0	0
X	0	4	0	1	3	1	1	1	1	0	0	0
XI	1	3	0	4	1	0	1	0	0	0	0	0
XII	0	2	0	1	3	0	1	0	0	0	0	0
XIII	0	2	0	0	1	1	1	0	0	0	0	0
XIV	2	2	0	3	5	2	4	1	2	0	1	0
XV	0	0	0	0	0	0	0	0	0	0	0	0
XVI	0	0	0	0	0	1	0	0	0	0	0	0
XVII	0	1	0	0	4	0	1	0	0	0	0	0
XVIII	1	2	1	0	4	0	3	3	1	0	0	2
XIX	2	2	0	1	3	0	0	1	0	2	0	2
XX	0	2	1	0	1	0	2	0	1	1	2	1
XXI	0	0	3	0	0	0	2	0	0	0	0	0
XXII	0	1	0	1	3	0	1	0	0	0	0	0
XXIII	0	0	0	0	0	0	2	1	0	0	0	1
XXIV	0	0	0	0	0	0	0	0	0	0	0	0
XXV	0	1	0	0	0	0	1	0	0	0	1	0
XXVII	0	0	0	0	0	0	0	1	1	0	0	0
XXVIII	0	1	0	0	0	0	0	0	0	0	0	0
XXIX	1	0	1	0	1	0	1	0	0	0	0	1
XXXI	0	0	0	0	0	0	0	0	1	0	0	0
XXXII	0	0	0	0	0	0	0	0	0	0	0	0
Neg. I–XX	0	1	0	1	4	1	0	1	0	0	0	0
Neg. I–XXXII	0	0	1	0	0	0	0	0	0	0	0	0
TOTALS	75	66	37	65	247	59	96	30	33	35	16	36

* These include the following:
Endocarditis 3 cases (Types I, VIII and X, 1 each);
Purulent arthritis 3 (Types I, XII, XIV, 1 each);
Osteomyelitis 7 (Type II, 2 cases; Types I, VIII, XI, XIX, XXII, 1 each);
Acute sinusitis 6 (Types II and VIII, 2 each; Types I, VI, 1 each);
Pulmonary abscesses 4 (Types III and V, 2 each);
Subcutaneous abscesses 10 (Type III, 3; Types II and XI, 2 each, and Types VII, VIII and XIV, 1 each);
Puerperal sepsis 3 (Type I, 2 and Type VIII, 1);
Bacteremia (positive blood culture, source not discovered) 18 (Types I and VIII, 4 each; Types II and III, 3 each; Types IV, VI, XI and Neg. I to XX, 1 each).
Also one case each of: Pericarditis, Type I; Infected hemothorax, Type I; Acute cystitis, Type III; Acute cholecystitis, Type III; Peritonsillar abscess, Type III; Mediastinitis, Type III; Subphrenic abscess, Type III; and Ulcerative colitis, Type IV.

† The following are not listed:
Arthritis 8 cases (Type I, 5; Type II, 1 and Type III, 2);
Parotitis 6 (Type I, 4; Types II and III, 1 each);
Conjunctivitis 4 (Type II, 1; Type III, 2; Type VIII, 1);
Liver abscess 1 (Type XI).
Empyemas in children and those present on admission in adults are listed in table 2 (*D* and *B*).

Focal Purulent Pneumococcic Infections

The numbers of cases in which each of the various types of pneumococci were cultured from focal infections, including those complicating pneumonia, are shown in table 4. Middle ear and mastoid infections were the most common in the cases without pneumonia, the Type III pneumococcus being the causative organism in about half of these cases. Meningitis, with or without middle ear or mastoid infection, was next in frequency and peritonitis ranked third. Of interest are the 18 cases of bacteremia, mentioned in the footnote to the table, in which neither pneumonia nor purulent foci were found even at the autopsy, which was performed in almost all of these cases.

Among the cases of pneumonia in adults, empyema was the most frequent purulent complication. Type I was most frequent in these cases as it was in the empyemas of children and in the adults who had empyema at the time of admission to the hospital (table 2). Lung abscesses or focal areas of necrosis were next in frequency, the most common organism being the Type III. Almost all of these were first observed at autopsy and a large proportion were seen only in the microscopic sections. The pneumococci in the latter cases were obtained from the infected lung. Pericarditis ranked third in frequency and, like endocarditis, was usually diagnosed at autopsy.

Pneumonia in Adults

The percentage of incidence and of mortality among the pneumonias caused by the more frequent of the pneumococcus types is analyzed in table 5 with respect to three important features, each of which may be considered separately.

Lobar Pneumonia and Atypical Pneumonia. There were cases of lobar pneumonia and of atypical pneumonia due to almost every one of the pneumococcus types (table 2). About one-fifth of all the cases of pneumococcus pneumonia had only atypical pulmonary consolidation. Types I and II stand out from among all the others as causing typical lobar pneumonia with the greatest regularity. Only 4 and 5 per cent of the cases of pneumonia due to these types, respectively, had only atypical involvement, and an additional smaller number of cases with lobar pneumonia due to these types had atypical consolidation in other portions of the lung. Among the other frequent types, more than two-thirds of the cases due to Types III, IV, V, VII, IX, XII, and XIV were lobar pneumonia, whereas about one-half of those caused by Types VI, X, XVII, XVIII, XX, and those with higher type designations were atypical.

The mortality was considerably higher among the cases with atypical pneumonia. This was true for all the cases, as well as for the cases within each type, the only exceptions being those with the Type III pneumococcus. Bacteremia was only half as frequent among the cases with atypical pneumonia as among those with lobar pneumonia. On the other hand, almost

TABLE V

Pneumococcus Pneumonia in Adults (Over 12 years of age)
Analysis of the relative incidence and mortality, for each type, of:
(1) Lobar pneumonia and atypical pneumonia, (2) So-called secondary pneumonia, and (3) Bacteremia

Type of Pneumococcus *	Lobar Pneumonia										Atypical Pneumonia									
	Number of Cases	Mortality (Per cent)						Incidence (Per cent)		Per Cent of Cases that Were Atypical	Number of Cases	Mortality (Per cent)						Incidence (Per cent)		
		All Cases	Blood Culture Positive	Blood Culture Sterile	Blood Culture Not Done	Primary	Secondary	Bacteremia ‡	"Secondary"			All Cases	Blood Culture Positive	Blood Culture Sterile	Blood Culture Not Done	Primary	Secondary	Bacteremia ‡	"Secondary"	
I (No serum)	365	43	79	21	21	41	66	42	7	4	28	89	100	89	91	50	96	55	86	
(Serum)	289	18	38	10	3	18	21		—	—	0									
II (No serum)	165	44	70	19	45	43	56	43	4	5	15	80	100	80	71	100	79	38	93	
(Serum)	129	25	51	9	30	23	100	—	—	—	0									
III	335	61	98	34	60	59	71	42	16	23	99	59	100	51	49	32	72	29	66	
IV	46	39	92	18	25	40	25	33	9	28	18	67	100	60	50	67	75	29	75	
V (No serum)	167	42	81	17	36	39	83	40	6	14	30	67	100	64	40	54	76	45	57	
(Serum)	24	17	43	6	—	17	—	—	—	—	0									
VI	28	39	100	43	17	38	50	5	14	52	30	50	50	73	23	10	70	12	67	
VII (No serum)	100	33	88	17	6	24	87	26	13	20	30	57	100	52	25	27	87	19	50	
(Serum)	28	7	20	4	—	4	50	—	—	—	2	50	—	50	—	50	—	0	0	
VIII	159	24	49	14	13	21	47	35	12	30	68	60	80	50	65	36	74	24	63	
IX	30	30	67	20	0	28	40	23	17	28	12	50	100	50	33	43	60	11	42	
X	37	32	75	33	17	32	33	16	24	52	40	50	100	68	0	18	62	11	70	
XI	29	24	75	20	10	21	100	21	3	38	18	44	—	47	33	0	80	0	56	
XII	38	29	80	14	0	24	75	31	11	17	8	63	100	50	0	67	60	43	63	
XIV	51	39	86	21	23	39	40	37	10	32	24	50	100	53	33	40	57	6	58	
XVII	19	26	—	38	0	8	57	0	37	51	20	40	—	42	38	38	42	0	60	
XVIII	38	29	100	20	0	27	40	26	13	46	32	66	100	65	50	30	82	23	69	
XIX	19	26	100	10	29	13	75	17	21	39	12	8	—	13	0	0	14	0	58	
XX	36	17	—	14	20	10	60	0	14	49	35	46	83	44	31	31	55	27	63	
All others †	99	26	71	20	33	22	60	9	10	50	98	42	70	45	19	21	55	14	61	
All Cases	2229	36	72	19	29	33	60	36	10	22	619	55	92	54	38	31	68	22	64	
No Serum	1759	41	80	22	31	38	63	36	11											
Serum	470	19	42	9	10	18	36	34	5											

* Specific types are listed separately when there were more than 30 cases of pneumonia.
† Including cases in which the pneumococcus failed to agglutinate in sera of Types I to XX or I to XXXII.
‡ Calculated on the basis of patients having blood cultures made.

two-thirds of the former cases were secondary to other serious illnesses, as compared with only 10 per cent of the latter. The higher mortality among the cases with atypical pneumonia, therefore, is probably attributable to factors within the host rather than to difference in virulence of the organism. The much greater frequency of atypical pneumonias in persons over 70 years of age (17 per cent of all the atypical cases as compared with 5 per cent of the lobar pneumonias) lends further support to this view.

"Secondary" Pneumonia. As in previous studies,[3] cases occurring as terminal events or as acute episodes in the course of other serious illness and those complicating parturition, the puerperium, surgical operations, or other serious acute infectious diseases were called "secondary." All other cases, including those with antecedent simple infections of the upper respiratory tract, "grippe," influenza, or bronchitis were called primary. Among the cases with atypical pulmonary involvement, the secondary pneumonias were more than six times as frequent as among the cases with lobar consolidation. The mortality was about twice as great among the secondary as among the primary pneumonias. The greater incidence of secondary pneumonias thus serves to explain the greater mortality among the cases of atypical pneumonia.

Bacteremia. The percentage of cases of pneumonia in which pneumococci were cultured from the blood varied with the different types. Bacteremia was much less frequent among the cases with atypical pneumonia than among those with lobar pneumonia. In general the mortality among the cases of lobar pneumonia corresponded to the incidence of bacteremia,[5] but this was not true for all the types of pneumococci. The mortality among the bacteremic cases was uniformly higher, and averaged about twice as high as among those with sterile blood cultures. This was true irrespective of the character of the pulmonary lesion.

Serum treatment was carried out almost exclusively in cases of lobar pneumonia due to Types I, II, V, and VII. Only the gross mortalities are given here and indicate a reduction to about one-half the mortality in non-serum treated cases. The results of serum therapy in these cases are presented in greater detail in other publications.[3a, 6]

Age Incidence. The highest incidence of lobar pneumonia occurred in the fourth and fifth decades of life, declining rapidly thereafter; in the atypical pneumonias the peak was in the sixth decade and there was almost no decline in the next two decades. Among the cases of lobar pneumonia of the more common types, those due to Types II, V, and VII each showed their highest incidence in the fourth decade. Those due to Type III had a peak of incidence among the cases in the sixth decade of life, while the cases of Types I and VIII pneumococcus lobar pneumonia were most prevalent in the fifth decade.

‡ Calculated on the basis of patients having blood cultures made.

Mixed Infections

There were 424 cases of pneumonia in which, in addition to the pneumococcus of the type under which the case was classified, other pathogenic organisms were obtained. These were cultured from sputum or from other

Table VI
Mixed Infections

	Total Number of Cases	Other Organisms in Cases of Pneumonia								Cases Listed with Other Types	
		Other pneumococcus types	*Streptococcus hemolyticus*	*Streptococcus viridans*	*Staphylococcus aureus*	*Bacillus mucosus capsulatus*	*Hemophilus influenzae*	Tubercle bacilli	Miscellaneous	Pneumonia Cases	Cases without Pneumonia
I	74	23*	25	8	14	5	7	5	6	8	3
II	28	6	12	3	7	1	5	3	0	4	0
III	61	21*	21	6	14	6	14	0	3	19	1
IV	14	2	3	2	2	3	5	1	5	5	0
V	35	12	17	1	7	1	6	0	1	3	1
VI	14	2*	2	2	4	3	3	1	1	3	0
VII	22	6	9	3	8	0	7	3	1	0	1
VIII	29	11	11	1	3	1	3	3	2	8	3
IX	9	1	3	2	2	1	2	2	0	2	0
X	21	3*	8	0	8	1	5	3	2	8	1
XI	10	5	4	0	2	0	4	0	0	5	1
XII	6	0	0	0	2	1	4	0	0	1	1
XIII	4	0	1	0	1	1	0	2	0	1	0
XIV	13	2	3	2	1	1	4	2	0	3	0
XV	2	0	0	0	0	0	1	0	2	2	0
XVI	5	1	1	1	0	0	1	1	1	2	0
XVII	12	1	3	0	3	1	5	0	0	2	1
XVIII	11	2	3	2	4	0	4	1	1	5	0
XIX	7	0	4	0	2	1	1	0	1	4	2
XX	15	2	6	1	2	1	4	1	4	8	4
XXI	6	0	2	0	2	1	3	0	0	4	3
XXII	11	2	3	0	2	0	7	1	1	0	0
XXIII	4	0	1	0	1	0	2	0	1	1	0
XXIV	1	0	1	0	1	0	0	0	0	3	0
XXV	2	1*	0	0	1	0	0	0	1	0	0
XXVIII	2	0	0	0	0	1	0	0	1	0	0
XXIX	4	0	2	0	1	1	1	0	0	2	1
XXXI	0	0	0	0	0	0	0	0	0	2	1
XXXII	2	0	1	0	0	1	0	0	0	0	0
Neg. I–XX	—	—	—	—	—	—	—	—	—	1	0
Neg. I–XXXII	—	—	—	—	—	—	—	—	—	2	0
Total	424	103	145	34	94	32	98	29	34	108	24

* 1 case had pneumococci of 2 other types.

sources during the acute illness, early in convalescence or at autopsy. Pyogenic organisms other than pneumococci, when obtained from sputum, were listed only when they were predominant in a good specimen or when they were cultured from the heart's blood of an injected mouse. Only hemolytic

strains of *Staphylococcus aureus* were included. Tubercle bacilli were noted whenever they were recognized in stained smears of sputum or pulmonary exudate. The number of cases in which various organisms were obtained in the pneumonias due to the various pneumococcus types is shown in table 6.

In 103 cases multiple pneumococcus types were isolated, five of these cases yielding three distinct types. The most frequent other organisms were *Beta hemolytic streptococcus, Hemophilus influenzae, Staphylococcus aureus hemolyticus, Streptococcus viridans,* and *Bacillus mucosus capsulatus* (Friedländer), in that order. Occasional instances of focal infections with colon bacillus, *Bacillus welchii,* or other organisms were noted as complicating the pneumococcus pneumonia. In other cases, the pneumococcus pneumonias occurred as a complication of other infections during which the causative agent, notably typhoid and paratyphoid bacilli were cultured.

The number of cases of pneumonia in which each of the various pneumococcus types occurred as a mixed infection, is also shown in table 6. The last column gives the distribution of types among 24 instances in which two types of pneumococci were identified among cases without pneumonia.

The significance of the various organisms in cases of pneumonia with mixed infection varies with each case. This has been discussed elsewhere.[7]

Comment

Type-specific antipneumococcic serum, within its limitations, is the only curative agent thus far recommended for the treatment of pneumonia which has stood the tests of experience, experiment, and critical analysis. The extension of serological typing to include practically all strains of pneumococci,[1] and the studies of the prevalence of these new types in health [8] and disease,[1, 2, 9] in addition to its great importance for the better understanding of the clinical, immunologic, and epidemiologic features of pneumococcic infections, has already proved useful in extending the field of specific serum therapy and holds promise for further practical benefits. Bullowa [10] has reported favorable results in the treatment of cases of pneumonia due to Types VII, VIII, XIV, and V pneumococci, and equally promising results were observed in the treatment of small groups of cases of Type V and Type VII pneumococcus pneumonia in this clinic.[6d, e]

It was not possible, in the space available, to analyze the material in any greater detail or to discuss the many possible implications of the findings recorded. Some of the clinical features of the more common types [3] and the details of specific therapy [6] in the present cases have been considered elsewhere. Other features of selected groups of cases, as well as the comparative significance of organisms other than the pneumococci [7] are left for separate consideration. It is hoped that the material here presented will help somewhat in the orientation of those interested in this rather extensive field of pneumonia and pneumococcic infections.

SUMMARY

A series of 3682 cases is presented from which specific types of pneumococci were obtained and classified with the aid of the newer serums of Cooper.[1] These cases occurred at the Boston City Hospital between November 1929 and June 30, 1936.

The incidence of the various types in different seasons and in different diseases and particularly in lobar pneumonia and atypical pneumonia (bronchopneumonia) is indicated.

The mortality rates in the cases of pneumonia in adults is noted with respect to: (1) The type of infecting pneumococcus; (2) the character of the pulmonary lesion; (3) the presence of bacteremia; (4) the presence of other serious illness (secondary pneumonias); (5) serum therapy.

The incidence of mixed infections with pneumococci and other significant organisms is shown.

BIBLIOGRAPHY

1. (*a*) COOPER, G., EDWARDS, M., and ROSENSTEIN, C.: The separation of types among the pneumococci hitherto called group IV and the development of therapeutic antiserums for these types, Jr. Exper. Med., 1929, **xlix**, 461.
   (*b*) COOPER, G., ROSENSTEIN, C., WALTER, A., and PEIZER, L.: The further separation of types among the pneumococci hitherto included in Group IV and the development of antisera for these types, *Ibid.*, 1932, lv, 531.
2. SUTLIFF, W. D., and FINLAND, M.: The significance of the newly classified types of pneumococci in disease: Types IV to XX inclusive, Jr. Am. Med. Assoc., 1933, ci, 1289.
3. (*a*) SUTLIFF, W. D., and FINLAND, M.: Type I pneumococcic infections with especial reference to specific serum treatment, New Eng. Jr. Med., 1934, ccx, 237.
   (*b*) FINLAND, M., and SUTLIFF, W. D.: Infections with pneumococcus Type III and Type VIII: Characterization of pneumonia caused by pneumococcus Type III and that associated with a biologically closely related organism, pneumococcus Type VIII, Arch. Int. Med., 1934, liii, 491.
   (*c*) FINLAND, M., and DOWLING, H. F.: Pneumococcus Type II and Type V infections, *Ibid.*, 1936, lviii, 598.
   (*d*) FINLAND, M., RUEGSEGGER, J. M., DOWLING, H. F., and TILGHMAN, R. C.: Infections with pneumococcus Type VII, Am. Jr. Med. Sci., 1937, cxciii, 48.
4. COLE, R. I.: Acute pulmonary infections, De Lamar Lectures, 1927–1928, Williams and Wilkins Company, Baltimore.
5. (*a*) BULLOWA, J. G. M., and WILCOX, C.: Incidence of bacteremia in the pneumonias and its relation to mortality, Arch. Int. Med., 1935, lv, 558.
   (*b*) TILGHMAN, R. C., and FINLAND, M.: An analysis of the clinical significance of bacteremia in pneumococcus pneumonia, *Ibid.* (In press.)
6. (*a*) FINLAND, M.: Adequate dosage in the specific serum treatment of pneumococcus Type I pneumonia, Am. Jr. Med. Sci., 1936, cxcii, 849.
   (*b*) FINLAND, M., and SUTLIFF, W. D.: The specific serum treatment of pneumococcus Type II pneumonia, Jr. Am. Med. Assoc., 1933, c, 560.
   (*c*) FINLAND, M., and DOWLING, H. F.: The dose of antibody effective in the treatment of pneumococcus Type II pneumonia, Am. Jr. Med. Sci., 1936, cxci, 658.
   (*d*) FINLAND, M., and TILGHMAN, R. C.: Clinical and immunologic observations in cases of pneumococcus Type V pneumonia treated with specific antibody, New England Jr. Med., 1936, ccxv, 1211.

(*c*) FINLAND, M., TILGHMAN, R. C., RUEGSEGGER, J. M., and DOWLING, H. F.: Clinical and immunologic observations in cases of pneumococcus Type VII pneumonia treated with concentrated type-specific antibody, Am. Jr. Med. Sci., 1937, cxciii, 59.

7. FINLAND, M.: The significance of mixed infections in pneumococcic pneumonia, Jr. Am. Med. Assoc., 1934, ciii, 1681.
8. GUNDEL, M., and SEITZ, L.: Die Pneumokokkentypen in der gesunden Bevölkerung, Klin. Wchnschr., 1933, xii, 929.
9. (*a*) BULLOWA, J. G. M.: Voraussetzungen und Technik der Pneumoniebehandlung, Klin. Wchnschr., 1936, xv, 769.

   (*b*) NEMIR, R. L., ANDREWS, E. T., and VINOGRAD, J.: Pneumonia in infants and in children; a bacteriologic study with special reference to clinical significance, Am. Jr. Dis. Child., 1936, li, 1277.

   (*c*) RAIA, A., PLUMMER, N., and SHULTZ, S.: New types of pneumococci in the pneumonias of children, Am. Jr. Dis. Child., 1931, xlii, 57.
10. (*a*) BULLOWA, J. G. M.: Therapeutic value of specific Type VII (Cooper) antipneumococcic serum, Libman Anniv. Vols., 1932, i, 283.

    (*b*) Therapeutic pneumococcus Type VIII (Cooper) serum, Jr. Am. Med. Assoc., 1934, cii, 1560.

    (*c*) Pneumonia due to pneumococcus Type XIV (Cooper) and its treatment with specific antiserum, Jr. Clin. Invest., 1935, xiv, 373.

    (*d*) BULLOWA, J. G. M., and WILCOX, C.: Therapeutic serum for pneumococcus Type V (Cooper) pneumonia, Jr. Clin. Invest., 1936, xv, 711.

AN OUTBREAK OF TRICHINIASIS IN CENTRAL OHIO AND THE USE OF THE BACHMAN INTRADERMAL SKIN TEST *

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The infrequency with which trichiniasis is recognized in man restricts the opportunity to study this disease and makes it important to utilize all cases whenever possible for the investigation of the Bachman intradermal test.

The consumption of raw or inadequately cooked meat is more common in this country than is generally appreciated. While this is often done inadvertently, there are many who, from choice, eat raw sausages or other forms of pork deliberately, and these individuals constitute the majority of the more severe cases of trichiniasis.

The discovery and development of our knowledge of human trichiniasis has been reviewed recently, notably by McDonald,[1] and this will not be discussed here.

In the state of Ohio trichiniasis is not rare, although it is not often recognized. Doran [2] states that only two cases have appeared at St. John's Hospital, Cleveland, Ohio, in the past 16 years. At Grant Hospital, Columbus, Ohio, we could find records of only one case since 1925. The disease has been reportable to the Ohio State Department of Health since August 1928. From this date until March 1936, 96 cases have been reported, and of this number eight have died, a mortality of 8.33 per cent. The distribution of these cases is recorded in table 3.

Relatively few reports concerning the use of the Bachman test are to be found in the literature, in spite of the fact that Bachman [3] first described the method in 1928. As late as 1931 an epidemic was reported in Pennsylvania by Aldridge [4] with no mention of the test.

Bachman describes the preparation of his antigen thus: "The larvae are separated by artificial digestion and thoroughly washed free from host proteins—dried at 47° C. in a vacuum oven over sulphuric acid and thoroughly pulverized. Test antigen is prepared from a 1 per cent suspension of the dried pulverized trichinella powder extracted at room temperature for a day or longer in Coca's solution—then centrifuged at high speed for 15 minutes and the supernatant fluid used as the test antigen."

The powdered trichinella material is not available commercially at the present time.†

The antigen we used was prepared at Grant Hospital by O. H. Lausa. His technic was as follows: "Take 5 mg. of the dried trichinella powder.

* Received for publication June 20, 1936.

† We wish to thank Dr. Benjamin Schwartz of the United States Department of Agriculture for supplying the necessary material.

Add 5 c.c. of Coca's solution and allow to stand at room temperature for 24 hours. Then filter through a Berkefeld filter. Culture to test for sterility. Place in vaccine ampoules for use." The pH was about 8.

Case Reports *

These cases will be divided into two sections. The first section will comprise the epidemic group, the second will be individual cases occurring at the same time in Columbus with different sources of infection.

Table I

Data on Cases of Diagnosed Trichiniasis

Case	Ingestion of pork	Onset of symptoms	Eosinophilia		Bachman Intradermal Test		
			Admission	10 days later	1–1000	1–10,100	Control
Section I							
1. C. M...	Dec. 24–Jan. 10	Jan. 8, 1936	5%	31%	++	+	0
2. E. B....	Jan. 1, 1936	Jan. 4, 1936	70%	43%	++	+	0
3. L. E....	Dec. 24, 1935	Dec. 28, 1935	33%	57%	++	+	0
4. R. B....	Dec. 24, 1935	Dec. 28, 1935	51%	20%	++	+	0
5. M. T...	Jan. 1, 1936	Jan. 4, 1936	47%	67%	++	+	0
6. E. T....	Jan. 1, 1936	Jan. 4, 1936	21%	32%	++	+	0
Section II							
1. C. H...	June '35–Jan. '36	Jan. 14, 1936	72%	?	+++	++	0
2. G. R...	Jan. 5, 1936	Jan. 14, 1936	31%	85%	+++	++	0

Table II

Control Tests

Case No.	Race	Diagnosis	Age	Eosinophile count	Bachman Skin Test		
					1–1000	1–10,000	Control
1. W. K.	W	Gastric carcinoma	83	0	0	0	0
2. L. R.	Eth.	Chronic heart disease	45	2%	0	0	0
3. H. T.	Eth.	Luetic aortitis	56	2%	0	0	0
4. C. F.	Eth.	Gangrene of toe	69	0	0	0	0
5. M. B.	W	Rheumatoid arthritis	47	0	0	0	0
6. L. L.	W	Chronic cardiac disease	40	4%	++	+	0
7. L. A.	W	Broncho-pneumonia	72	0	0	0	0
8. E. I.	W	Cardio-vascular renal dis.	49	1%	0	0	0
9. I. G.	W	Malignancy of cervix	63	0	0	0	0
10. W. R.	W	Arteriosclerosis	64	4%	0	0	0
11. W. B.	W	Tabes dorsalis	30	0	0	0	0
12. J. C.	W	Ascites	74	2%	0	0	0
13. J. H.	W	Hypertrophic arthritis	79	0	0	0	0

* I wish to thank Dr. C. Joseph DeLor of University Hospital and Dr. Thomas E. Rardin and Miss Marcella Huercamp of St. Francis Hospital for their help in the making of these tests and the presentation of the case reports.

TABLE III

Cases of Trichiniasis Reported in Ohio

County	1929	1930	1931	1932	1933	1934	1935	1936	Total
Allen	4								4
Auglaize				1	8		7		16
Belmont	4								4
Cuyahoga	5	1	3	15	1	6	9		40
Darke							5		5
Erie					1				1
Jefferson						1		4	5
Mercer							3		3
Montgomery						1			1
Preble							1		1
Putnam								3	3
Shelby							10		10
Miami					1		2		3
Total	13	1	3	16	11	8	37	7	96

Deaths from Trichiniasis in Ohio

County	1931	1932	1933	1935
Darke				2
Franklin		1	1	
Hamilton			1	
Summit	1			
Trumbull		1		
Williams	1			

SECTION I

About December 20, 1935, a 300 pound hog was butchered by a packing company in central Ohio. The meat was inspected and passed by an inspector. All of the cases to follow in this section ate the pork in a raw state prior to December 25, 1935 except C. M. who continued to eat it up to January 10, 1936 cooked " very rare."

Case 1. Mr. C. M., a white male 22 years of age, whose occupation was dairyman, was admitted to University Hospital on January 11, 1936 complaining of generalized malaise, pain in the back, fever and sweating.

Physical examination revealed edema of the eyelids, bilateral conjunctivitis and photophobia. There was marked generalized muscular pain, but other than this the physical examination was essentially negative. His temperature upon admission was 104.2° F., pulse 115, and respirations 38. A blood count revealed hemoglobin 85 per cent, erythrocytes 4,820,000, leukocytes 16,450; 67 segmented, 16 band, 10 lymphocytes, 2 monocytes, and 5 eosinophiles.

Biopsy of the gastrocnemius muscles near the tendinous attachment revealed severe myositis and larvae of *Trichinella spiralis.*

During the course of his stay in the hospital the leukocytes varied between 10,800 and 19,750. The highest eosinophile count was 31 per cent, and it is significant to note that the highest eosinophile counts were noted with the lowest total counts. Agglutination tests for typhoid fever, undulant fever, and tularemia were negative. The cerebro-spinal fluid was normal.

Treatment was symptomatic except for the use of neoarsphenamine which had no apparent effect. The patient was discharged from the hospital February 4, 1936 apparently in good condition except for considerable loss in weight.

Case 2. E. B., a white female 27 years of age, was admitted to St. Francis Hospital on January 14, 1936 complaining of severe pain in all the extremities, fever, diarrhea, generalized edema and sore throat.

About two weeks previous to admission she had eaten some raw pork and two or three days later first noticed a diarrhea. This continued for several days, and then she became constipated. The patient then developed severe muscular pains in all extremities with accompanying generalized edema, particularly under the eyes. She also had laryngitis which persisted for a few days. No glandular enlargement or swelling, and no vomiting were noted.

The physical examination revealed a white female, acutely ill and prostrated, with marked edema of legs and arms. The skin was anemic, dry and hot. There was marked edema under the eyelids. The throat was much injected and dysphagia pronounced. The heart was normal except for a rapid rate.

On admission her eosinophiles were 70 per cent, and 10 days later, 43 per cent.

Case 3. L. E., a white male 30 years of age, was admitted to St. Francis Hospital on January 14, 1936. Several weeks previous to admission he had eaten some raw pork. Soon after this he became quite ill and began to have diarrhea. He took a dose of epsom salts, and soon the symptoms began to subside, although edema of the eyelids developed. Diarrhea stopped and constipation was noted. Muscular pains were moderately severe. No nausea, vomiting, or cough.

Physical examination revealed a white male, not acutely ill and in no apparent distress. The skin was negative except for slight redness and edema of the eyelids. Examination was otherwise negative.

On admission his eosinophile count was 33 per cent; 10 days later it was 57 per cent.

Case 4. R. B., a white boy eight years of age, was admitted to St. Francis Hospital on January 14, 1936. This child ate some raw pork with other members of the family several weeks previous to admission. He became acutely ill, with cramps, diarrhea, and generalized edema. Severe muscular pains were present.

Physical examination revealed a white male child, apparently acutely ill with some evidence of prostration. The skin was negative. The eyes were negative except for slight edema of the eyelids. The examination was otherwise negative.

On admission the patient had 51 per cent eosinophiles; 10 days later they were 20 per cent.

Case 5. M. T., a white female 24 years of age, was admitted to St. Francis Hospital on January 14, 1936. At this time her temperature was 103° F. (rectal) and she complained of pain in the extremities. She gave a history of having eaten raw pork about two weeks previous to her admission to the hospital. Shortly after, she began to develop intestinal symptoms followed by diarrhea. This was soon checked. The patient then developed edema of the eyelids but was relatively free from edema elsewhere. Pains were not particularly severe. She had no nausea or vomiting. She had had a mild fever for two weeks previous to admission.

Physical examination revealed a white female, apparently in no great distress, showing some puffiness of the eyelids. The skin was pale and anemic. The eyelids were slightly edematous with an area of redness around the orbit. Otherwise negative.

On admission she had an eosinophilia of 47 per cent; 10 days later it was 67 per cent.

Case 6. E. T., a white female child three years of age, was admitted to St. Francis Hospital on January 14, 1936 with pain in the extremities, edema, and fever.

The history was similar to those of the cases above. She developed edema of the eyelids, some diarrhea with occasional vomiting, and a fever of 103° F., rectal.

Physical examination revealed a white female child, acutely ill, and somewhat dehydrated, who apparently had had a high fever for some time. The eyelids showed some evidence of edema. The abdomen was slightly rigid, somewhat tympanitic, slightly tender over the spleen and liver. Otherwise negative.

On admission she had an eosinophilia of 21 per cent; 10 days later the count was 32 per cent.

Section II

Case 1. C. H., a white male 22 years of age, was admitted to University Hospital, January 24, 1936, complaining of swelling of the eyelids, generalized muscular weakness and malaise. The patient gave a history of having eaten improperly cooked hamburgers frequently during the past six months or year. The present symptoms appeared seven days prior to admission. He also complained of nausea, vomiting, diarrhea, and a conjunctivitis. He was seen at the Student Health Service on the campus of Ohio State University and was referred to the hospital with a diagnosis of trichiniasis.

Upon admission the eosinophile count was 72 per cent. His temperature was 102.4° F.

Case 2. G. R., a white female 12 years of age (author's case), gave a history of having eaten some rare roast pork (purchased from a chain grocery store) about January 5, 1936, and a day or so afterwards she ate some rare side meat of pork from the same source. About January 14 she first noticed that her eyelids were markedly swollen, especially in the morning. They seemed to recede somewhat at night. On January 16 she began to have cramp-like pains in the muscles of her legs, severe enough to cause her to flex her legs. Extension of the legs was very painful. Her temperature at this time was 102.2° F., pulse 128 and regular. No signs of meningitis were present. A blood count showed an eosinophilia of 31 per cent. A diagnosis of trichiniasis was made. On January 21 calcium gluconate with haliver oil and viosterol was started. The apparent effect of this therapy on the fever encourages us to believe that it may have brought about a shortening of the encystment stage.

Control Tests

The Bachman skin test was given to a series of patients in St. Francis Hospital who were admitted because of some other disease and who presented no obvious symptoms of trichiniasis. Table 2 shows the results of these control tests. All of the tests were entirely negative except one (L. L.) which was as strongly positive as any of those obtained in the cases tested in Sections I and II. This patient (L. L.) gave a history of having eaten raw sausage sandwiches over a period of years and gave a vague history of muscle pains which were believed to be arthritic. She remembered no edema. Her blood count at the time of the test showed 4 per cent of eosinophiles. In view of these findings and her history we regard this as an unrecognized case of trichiniasis discovered by the Bachman test.

Comment on Skin Tests

The results from the use of the Bachman test have been quite favorable when used and read correctly. Goldschlager [5] reports a series of eight cases

all positive to the test. All of his controls were negative except one which he attributes to a phenol sensitivity. Drake,[6] in a series of 24 cases in which the tests were satisfactorily applied, reports all positive or 100 per cent. In 25 cases that had eaten the infested meat and gave no history of illness but had eosinophilia, only 12 reacted positively to the test, about 50 per cent. McCoy[9] selected 88 patients that had had the infestation within the past eight years. Of 36 of these who had been ill two to six weeks, 31, or 92 per cent, gave a positive test. Of 39 tested from three to 22 months after infestation, 31 or 80 per cent were found to be positive. Of 13 persons ill three and a half to seven and a half years prior to the test, a total of eight or 62 per cent were positive. He also adds that in 539 tests only seven persons were found to be sensitive to the control injection. Summarizing the above experience (and excluding all cases of McCoy's tested more than six weeks following infestation) the tests were positive in about 95 per cent of the cases.

Our experience with the Bachman test has been very satisfactory. We believe it is as efficient as the average diagnostic skin tests in other fields. We obtained positive reactions in every one of our small series of cases (table 1). The accuracy of the test depends upon securing a suitable preparation of powdered larvae and properly preparing the antigen solution from the powder. At present there is no adequate supply of the material available. New antigen must be prepared frequently. If kept on ice, it is reported to retain its potency for about six months. If not kept on ice it deteriorates much more rapidly. We found one such preparation inert after two months. We believe the commercial production and distribution of powdered trichinella larvae for antigen would be a definite service to the profession.

We did not utilize the Bachman precipitin test[8] in this study. This test usually does not become positive until three or four weeks after infection. However, it would aid in detecting border-line cases which are of greater duration than this. Bachman,[10] in a report of his work in Puerto Rico, showed that this precipitin test is 90 per cent specific.

Conclusions

1. Eight cases of trichiniasis with recovery are reported which were all positive to the Bachman intradermal skin test.

2. A résumé of the incidence of the disease in Ohio shows 96 cases in the last eight years with a mortality of 8.33 per cent.

3. The Bachman intradermal skin test is a valuable diagnostic aid in trichiniasis and should supplant the biopsy of muscle.

BIBLIOGRAPHY

1. McDonald, E. P.: An epidemic of trichinosis, Jr. Am. Med. Assoc., 1929, xcii, 449–453.
2. Doran, F. J.: Trichinosis, Ohio State Med. Jr., 1935, xxxi, 267–268.

3. Bachman, G. W.: Intradermal reaction in experimental trichiniasis, preliminary report, Jr. Prev. Med., 1928, ii, 169–173.
4. Aldridge, F. C.: An outbreak of trichinosis in Pennsylvania, Am. Jr. Med. Sci., 1931, clxxxi, 312–323.
5. Goldschlager, A. I.: A report of eight cases with skin and precipitin tests, Ann. Int. Med., 1935, viii, 939–950.
6. Drake, E. H., Hawkes, R. S., and Warren, M.: An epidemic of trichinosis in Maine, Jr. Am. Med Assoc., 1935, cv, 1340–1343.
7. Weiss, M.: Trichinosis—recent observations, N. Y. State Med. Jr., 1929, xxix, 1113–1116.
8. Bachman, G. W.: Precipitin test in experimental trichinosis, Jr. Prev. Med., 1928, ii, 35–48.
9. McCoy, O. R., Miller, J. J., and Friedlander, R. D.: Use of intradermal test in diagnosis of trichiniasis, Jr. Immunol., 1933, xxiv, 1–23.
10. Bachman, G. W., Molina, R., Rodriguez, G., and Jose, O.: Anomalous and nonspecific reactions with trichina antigen in relation to other disease conditions, Proc. Soc. Exper. Biol. and Med., 1934, 32–96.

CHRONIC ULCERATIVE COLITIS: FACTORS INFLUENCING ITS RESPONSE TO SPECIFIC TREATMENT *

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KNOWLEDGE of the condition that is known as "chronic ulcerative colitis" seems to date at least to the "bloody flux" of Sydenham, in 1669.

Its bacterial etiology has been recognized only recently. Etiologic significance has generally been ascribed to the diplostreptococcus originally described by one of us.

The similarity of this disease, because of its destructive character, to tuberculosis has frequently been emphasized. This fact has made it difficult to evaluate any single therapeutic agent employed in its treatment. Even though many clinicians seem to recognize its similarity to tuberculosis they frequently have not comprehended the importance of a therapeutic regimen similar to that generally accepted for tuberculosis. A carefully regulated and properly organized program of management for this disease cannot be overemphasized. It was with this thought in mind that the study recorded here was undertaken. We have tried to evaluate the part played in this program by our serum therapy or specific therapy.

Two of the major efforts in the treatment of this disease have been to immunize victims of this disease against the diplostreptococcus of colitis and to remove sources distant from the colon that might harbor this organism. Results of cultures of the rectal discharges of these patients have been recorded. An attempt has been made to correlate the incidence of positive culture and the immediate result of treatment.

We have reviewed the cases of chronic ulcerative colitis in which treatment was given during a given period of time to see whether response to treatment varied in the cases in which the diplostreptococcus was found and in those in which the culture of the rectal discharges was reported as negative. Table 1 will illustrate the degree of immediate improvement following our program of management, which included as one of its major efforts the administration of the serum. It will be noted that the patients failed to respond to treatment in only 11 per cent of the cases. These were all cases in which all objective tests lead to the diagnosis of chronic ulcerative colitis or colitis gravis, the type in which the diplostreptococcus is usually found. Grade 1 improvement refers to the group in which there was a slight but unsustained improvement. Grade 2 refers to moderate but continuous improvement, and grade 3 refers to marked improvement with relief of all symptoms and no exacerbation of symptoms up to the time of this review. Grade 4 refers to complete and prompt relief of all symptoms. The latter

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TABLE I

Degree of Improvement in 181 Cases of Chronic Ulcerative Colitis

Culture for Diplostreptococcus of Colitis	Grade of Immediate Improvement Following Treatment										Total
	0		1		2		3		4		
	Cases		Cases		Cases		Cases		Cases		
	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	
Positive	7	8	9	10	38	43	20	23	14	16	88
Negative	14	15	16	17	35	37	18	20	10	11	93
Total	21	11	25	14	73	40	38	21	24	13	181

group can truly be called healed. A review of this table will promptly suggest that there is no material difference in the response of patients with "positive" cultures and those with "negative" cultures. One might be inclined to infer from this that the improvement which follows treatment is unrelated to the presence of the diplostreptococcus. However, a review of table 2 will promptly dispel such an inference. It will be seen how difficult it is to call a culture "negative" until repeated cultures have been attempted.

TABLE II

Number of Cultures Attempted in 259 Cases before a Positive Culture Was Obtained or a Negative Culture Was Declared

Results of culture	Number of cultures						Number of cultures not analyzed	Total
	1	2	3	4	5	5+		
Positive	86	12	5	2	2	1	35	143
Negative	44	25	19	11	5	12		116

Table 2 presents a review of the number of attempts to culture the rectal discharges of each patient. The number of patients studied in the two series do not correspond in all details because, as would seem obvious, not all patients who have any type of disease can be accurately controlled. The 259 patients represent those who were observed for more than a year.

Table 3 illustrates the amount of bowel involved in a group of 172 cases. The extent of involvement has been graded 1, 2, 3, and 4, corresponding roughly to the four segments of the bowel; that is, involvement, grade 1,

signifies that the process is confined to approximately a fourth of the length of the large bowel. In these cases the involvement was predominantly in the rectum and sigmoid colon, but in a few instances it was only in the cecum and ascending colon or only in the descending or transverse colon. Grade 4 involvement signifies involvement of the entire colon, no special designation being given to those cases (18 in this series) in which roentgenologic examination revealed that there also was involvement of the terminal portion of the ileum.

TABLE III

Relation of Extent of Involvement to Grade of Improvement

Extent of involvement	Grade of improvement										Total	
	0		1		2		3		4			
	Cases		Cases		Cases		Cases		Cases			
	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent
1....	2	4.7	3	7	16	38	15	35	7	16	42	24.4
2....	3	19	3	19	4	25	5	31	1	6	16	9
3....	1	10	2	20	7	70	0	0	0	0	10	5.8
4....	13	12.5	15	14.4	45	43.2	19	18.3	13	12.5	104	60.4
Total .	19	11	23	13.4	82	46.5	39	22.7	21	12.2	172	

Study of table 3 reveals that the preponderant percentage of cases (60.4 per cent) falls into the group in which the involvement was grade 4; the others follow in the order 1, 2, and 3. Furthermore, it will be seen that no important relationship can be drawn between extent of involvement and degree of improvement. Patients whose entire colon was involved seemed to respond equally as well to treatment as did those who had involvement of only one segment.

Further study of these cases will reveal that, while the amount of bowel involved has no material relation to the response to treatment, the activity of the disease and the length of time a patient has been ill are definite factors which affect the response to treatment. Even though there is involvement of the entire large intestine, if the degree of activity of the disease is mild, the response to treatment is quicker and more actively sustained, the relief of symptoms is more likely to be complete than if the bowel is involved by more active disease. Obviously, when the disease has lasted for months or years, its continuous onslaught on the bowel will produce damage which may be irreparable. That the length of time the patient has had the disease bears

some relation to the response to treatment is illustrated by table 4. This table would suggest that the benefits to be expected from treatment of chronic ulcerative colitis bear an inverse ratio to the duration of the disease. No one can say just how large a part the administration of serum plays in the therapeutic response in these cases. The fact that relief is frequently dramatic, improvement is rapid, and progressive and complete restoration to normal occurs, suggests that the administration of serum plays a part in the improvement. The fact that improvement is usually slow, even though progressive, would suggest the importance of all the other accessory therapeutic endeavors.

TABLE IV

Relation of Grade of Improvement and the Duration of Symptoms before Treatment

Duration	Grade of Improvement										Total
	0		1		2		3		4		
	Cases		Cases		Cases		Cases		Cases		
	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	Number	Per Cent	
1 year or less...	7	11	6	10	20	32	12	19	17	27	62
1 to 5 years....	8	10	9	12	37	48	19	25	3	4	76
5 years or more.	6	14	9	21	16	38	7	16	4	10	42
Total.....	21		24		73		38		24		180

This review would further substantiate the opinion previously expressed that surgical interference in these cases should be confined to complications of the disease for many of the patients, even though they make but little immediate response, will in the course of months improve and finally the disease will be completely arrested as far as any intestinal symptoms are concerned.

Another interesting point concerning intestinal disorders was observed during the time that this series of cases of chronic ulcerative colitis was studied. In cases of diarrhea the patients were sent to the laboratory for culture of the stools. Table 5 illustrates the number of these cases in which the diplostreptococcus was found, but in which there was no objective evidence of chronic ulcerative colitis. These cases represent only a very small fraction of the cases of diarrhea in which cultures for this organism were made during the period of this study. Several of the patients in these cases passed blood later during an attack of acute pharyngitis. Others who had an irritable colon improved as a result of the administration of anticolitis

vaccine. Others experienced an attack of diarrhea following the administration of too large a dose of the vaccine. These observations would suggest a subclinical condition of colitis and would suggest the nature of treatment advisable in selected cases of this type.

TABLE V

Cases in Which the Diplostreptococcus Was Present without Objective Evidence of Chronic Ulcerative Colitis

Final Diagnosis	Cases
Irritable colon	16
Deficiency diarrhea	3
Subacute purulent appendicitis	1
Typhoid fever	1
Amebic dysentery	1
Diverticulosis	1
Tuberculous enteritis	1
Rectal abscess	1
Chronic infectious arthritis	1
Simple diarrhea	1

SUMMARY

The importance of a well-ordered program of treatment in cases of chronic ulcerative colitis cannot be overemphasized. When all objective tests point to a diagnosis of chronic ulcerative colitis, even though positive cultures for the diplostreptococcus are not obtained, specific treatment should be given. The number of attempts which should be made to culture rectal discharges and to culture the lesions directly through the proctoscope remains unsettled. In many cases in which the culture is reported "negative" on first culture, the culture will become "positive" on repeated cultures. This fact emphasizes the difficulties of making cultures of the stools and the importance of following details of a well-ordered technic.

Response to treatment varies inversely with duration of the disease and directly with its activity and severity. Patients who harbor the diplostreptococcus of colitis and who have diarrhea, even though they have no proctoscopic evidence of the disease, may be saved much trouble by undergoing treatment for subclinical types of colitis.

FURTHER OBSERVATIONS ON RAPID HYPOSENSITIZATION *

By G. L. WALDBOTT, M.D., F.A.C.P., and M. S. ASCHER, M.D.,
Detroit, Michigan

RECENT textbooks on allergy make only little mention of rapid hyposensitization † treatment and only a few clinicians have given this method serious consideration. The method of administering small increasing doses of antigen at short intervals was first introduced by Besredka [1] for the avoidance of serum reactions after he had observed that in animals the re-injection of a sublethal dose of antigen resulted in a temporary state of anti-anaphylaxis and that during this state larger doses of antigen could be more readily tolerated.

In 1930 Freeman [2] adopted this method of treatment for the relief of patients with hay-fever and asthma. His case reports, however, rather tend to discourage its application for clinical use. He was forced to add epinephrine to each injection because of the occurrence of severe constitutional reactions; yet, in spite of this precaution such reactions occurred. Tuft [3] and Blankenhorn [3] reported cases of shock and death following injections of horse serum in patients in whom desensitization had been attempted by giving increasing doses at short intervals.

For some time past, we have attempted to adapt this method to clinical application in allergic patients suffering from asthma and hay-fever. At first we met with little success because of the frequency of severe reactions. In a preliminary report [4] we concluded that this procedure was not devoid of danger. Our interest was greatly stimulated after we had begun to use co-seasonal treatment for hay-fever and asthma. This mode of treatment taught us two principles which we found to be the key to any form of hyposensitization, namely, to start with a sufficiently small dose and to gauge the dose of subsequent injections from the size of the local wheal obtained on the site of the previous one.

INDICATIONS

With co-seasonal treatment, we found as have Vaughan,[5] Phillips [5] and others that prompt relief from hay-fever can be established in many instances. The beneficial results, however, are often transient and in the severe cases inadequate (especially is this true in pollen asthma). If more lasting results are to be obtained it is essential to reach a higher final dose.

* Received for publication January 25, 1937.

† The term "hyposensitization" is used by some in order to indicate that "complete" *de*sensitization, as in an anaphylactic animal, is impossible in man. We do not believe that such a distinction is possible since in man no one has ever given, for the purpose of desensitization, doses corresponding even approximately to those given to an anaphylactic animal per kilogram of body weight. However, we shall adhere to the common nomenclature to avoid confusion.

Recent experience has convinced us that in severe chronic asthma in which the causative antigens are known this is the method of choice. Another main indication for this treatment exists in patients with hay-fever or asthma in whom the time for treatment is limited. It has also proved successful in cases of atopic eczema of known etiology. In cases of marked multiple sensitivity in which the diet was greatly restricted, it has been of great value to us in the effort to counteract sensitization to those antigens which were most important in keeping up the patient's nutritional state. We are particularly referring to rapid hyposensitization against such foods as milk, wheat and egg. Although we have only a limited experience with the prevention of "allergic" shock following therapeutic or prophylactic injections of animal serum, we believe that the principles advocated here are applicable to any form of serum therapy.

Technic

Our technic is as follows: The initial dose should be such that the resulting wheal from the injection will have subsided within 45 minutes. This can be accomplished if we use, for example, a dose as low as ½ Noon unit (0.0005 mg.) of pollen extract, in an average pollen case. In the more sensitive individuals this dose is reduced; in the less sensitive ones as high as 3 units (0.003 mg.) to 5 units (0.005 mg.) are given as the initial dose. This infers, of course, that the patient has actually been found to be sensitive to the specific antigen and that a larger dose will produce the usual local reaction. As a guide we routinely perform scratch tests at first. Should they be markedly positive (as in case 2, in which a scratch test with ragweed extract produced a generalized reaction), we repeat the tests after an interval of 15 to 20 minutes in order to establish local wheals repeatedly. After having thus produced moderate sized wheals one can more easily build up the first intradermal doses. As antigens we employed mostly pollen but also any of the other inhalants, foods, and other substances which we felt, by skin tests and clinical evidence, were of primary importance. We frequently used combinations of various antigens. No different therapeutic response was noted whether the injection was given intradermally or subcutaneously. The intradermal injections, however, because of the more distinct appearance of the wheal, were of greater service as a gauge for further treatment.

If the preliminary injections result in no, or little local whealing the subsequent ones may be given at very short intervals (10 to 15 minutes) and the increase may be from 50 to 200 per cent of the previous dose. After the desired wheal is obtained, the injections must be increased more slowly (from 10 to 30 per cent of the previous dose) and the intervals made longer (from 2 to 6 hours). If no swelling is obtained upon the rapid increase of doses and frequent injections the case should be re-investigated and search for other antigens be made.

If too large a swelling occurs or if an aggravation of the existing symptoms takes place, the treatment should be discontinued for 6 to 8 hours and then renewed with lower doses.

Reactions

Marked local edema at the site of injection may be indicative not only of an early reaction, if it appears rapidly, but also of a delayed "allergic" reaction. This may occur six to ten hours after the treatment had been administered. If an early constitutional reaction is encountered, we give no, or very little epinephrine (1/20 to 1/10 c.c.) as the use of epinephrine may mislead us in gauging the doses for the subsequent treatment. This is in contrast to the technic advocated by Freeman who administered epinephrine frequently together with the antigenic extract. After a generalized reaction has occurred we discontinue the injections for a given period and decrease the subsequent doses. In such a case it is sometimes desirable to stop the treatment for a whole day and to continue with smaller doses without a subsequent immediate increase.

In "intravenous" or "backseepage" reactions (Waldbott and Ascher[6]) which are evidenced by their immediate onset (within 10 seconds to a few minutes) and occasionally by bleeding upon the site of injection, epinephrine is, of course, indicated in large doses.

As a rule we do not set ourselves a definite goal as to the final dose. In the effort to reach too high a dose one may produce constitutional reactions and thus defeat the purpose of the treatment, namely, immediate improvement. We do, however, often reach a final dose as high as is customary in hyposensitization treatment.

Results

In discussing the results obtained, two questions should be dealt with separately. Firstly, is it possible to reach safely large doses in a relatively short period of time? Secondly, how does the improvement resulting from this treatment compare with that attained by other methods? Chart 1 presents data bearing on the first point from a group of seven consecutive cases and indicates that within a period of four to seven days, doses as high as 8000 units of pollen extract can be reached without untoward effect. It should be emphasized that all the cases included here were found definitely sensitive to the antigens administered. Even in cases in which constitutional reactions occurred relatively large doses could be reached as seen in chart 2.

In comparing end results with those obtained by other methods the question of proper controls is very complicated. Practically anything may "cure" an asthmatic at any time. Especially in the chronic asthmatic such measures as hospitalization, discontinuance of epinephrine or other drugs and such natural means of relief as the termination of a pollen season, of

a fungi season, of an infection, etc., may contribute to or induce a "cure." Furthermore, a patient apparently "cured" for a considerable period of time may at any time under certain circumstances have a flare-up of the previous disease merely because of an unusually heavy exposure to antigens to which a latent sensitivity may exist. That previously positive skin reac-

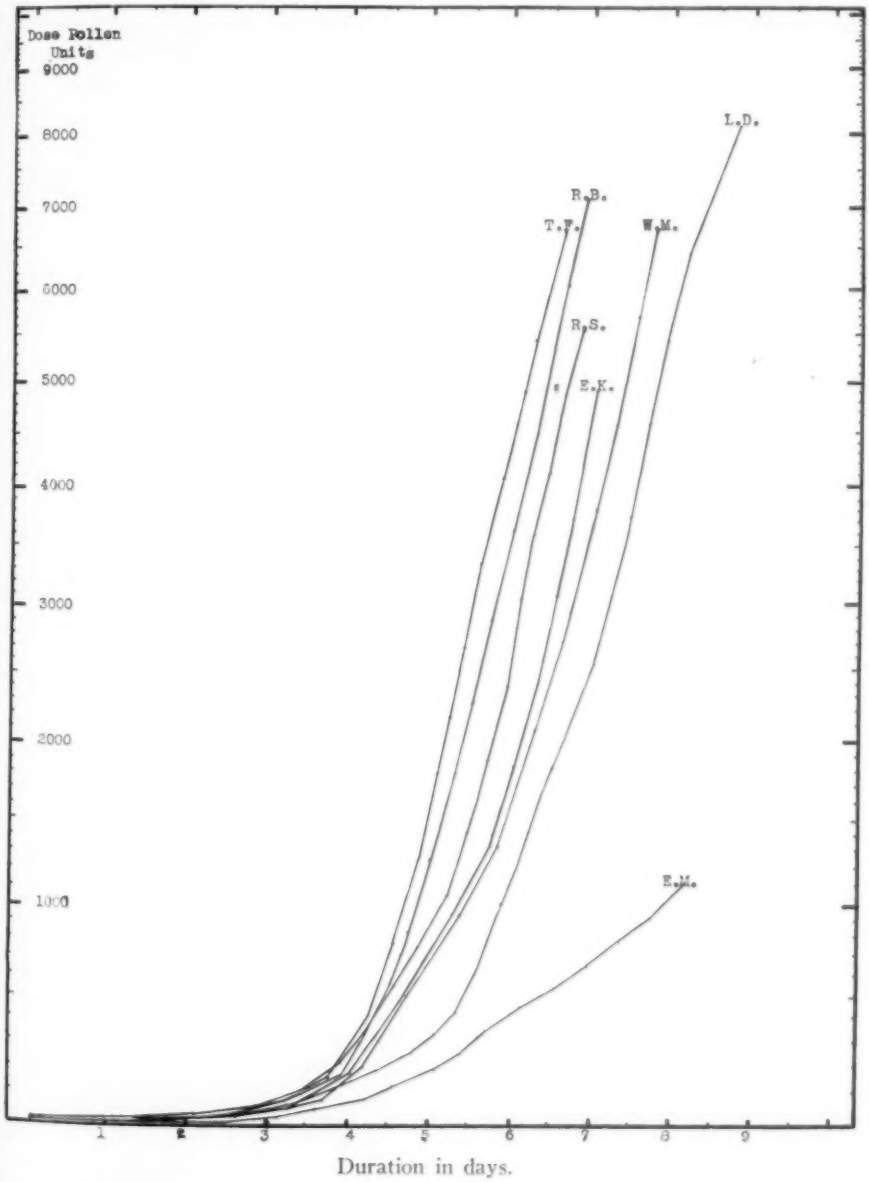

Chart 1 demonstrates how relatively high doses of extract can be reached in a short time in seven consecutive pollen cases.

tions become negative after administration of antigen at short intervals was recently shown by Rackemann and Wagner.[7] This, however, again cannot be considered a criterion of a "cure." To speak of a "percentage of cure," as it is often done, particularly in connection with hay-fever therapy, is again subject to the above objections.

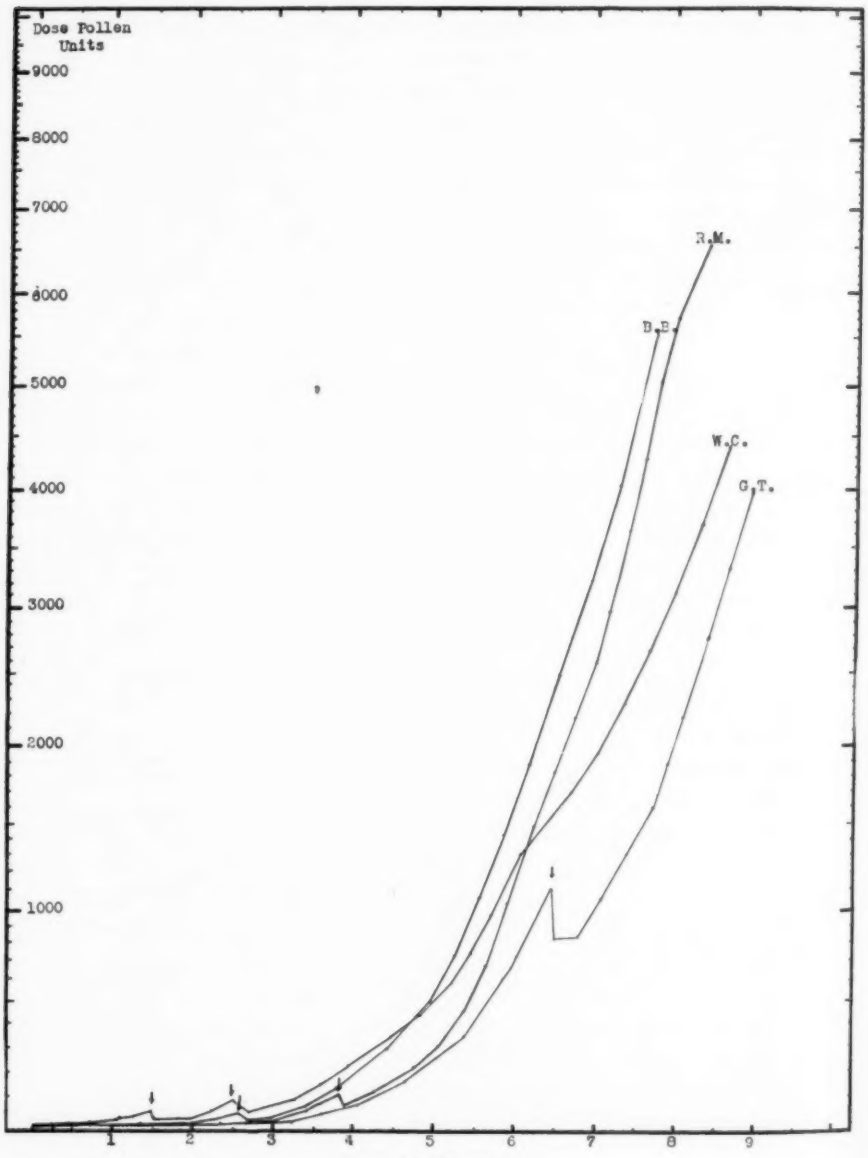

Chart 2 demonstrates the increase in doses following constitutional reactions in four selected pollen cases.

Conforming with the purpose and the indications of this method of treatment and the difficulties involved in establishing adequate methods of control, we therefore do not concern ourselves with the late effects of this treatment, but are merely recording the clinical improvement, i.e., the relief of symptoms noticeable during a period of several weeks. In the pollen cases of this series this period of time extended throughout the respective pollen season. All our patients were instructed to return to the office or to notify us immediately upon the return of any symptoms at any time. A recent follow-up on the cases included here, assured us that this instruction had been carried out and reaffirmed our previous opinion.

The treatment had been administered to more than 300 patients. Of these we selected 146 in whom we felt that as adequate a control as possible had been established. We are referring here to the discontinuance of other therapeutic measures, to the lack of success with such measures, to the length of time during which the patients had been under our observation before and after the treatment, as well as to the general trend of allergic symptoms as influenced by the climatic condition of the respective season. In these patients we, furthermore, had evidence to believe that the antigens used were the primary causative agents.

Among these 146 cases, there were 78 with hay-fever, 61 with asthma, or asthma combined with hay-fever, 7 with atopic eczema. Fifty-two became entirely free from symptoms, the improvement becoming noticeable immediately after the first few injections: 83 patients were considerably improved; 11 failed to respond to the treatment. Among the 83 patients who were "considerably improved," 21 had what we considered to be late reactions, which were evidenced by a temporary aggravation and which were followed by subsequent freedom from symptoms. With our advancing experience the number of these reactions has been reduced. Most of the asthmatics had been in a rather severe asthmatic state. Thirty-nine out of the 61 had to be hospitalized. Of these 39, only four failed to show definite improvement.

The following are the protocols of three representative cases:

Case Reports

Case 1. Mrs. F. B., aged 46, was admitted to Grace Hospital on June 4, 1936 at the height of the grass pollen season with a severe attack of bronchial asthma. She had been treated by such measures as epinephrine, ⅓ to 1 c.c., eight times a day, opiates, barbiturates, inhalation of stramonium powders, iodides by mouth and intravenously, and, at intervals of two to three days, injections with various antigenic substances to which she had shown positive reactions. In spite of this therapy the asthmatic state persisted. On the tenth day of admission all medication was discontinued. As no improvement took place during the two following days, 1 Noon Unit (0.001 mg.) of a combination of grass pollens (Orchard Grass, June Grass, Red Top, and Timothy) was given intradermally, after preliminary scratch testing had shown two to four plus reactions to these pollens. Subsequent injections with a moderate increase were given at three hourly intervals so that a dose as large as 4500 units (4.5

mg.) was reached on the fourth day. After the third injection there was a definite subsidence of the asthmatic symptoms. She was discharged from the hospital on the eighteenth day and remained under our observation for two more months, free from asthma.

Comment: This patient represents a typical instance in which hospitalization and other methods failed. Here a rather high dose of antigen was reached within a short time, giving prompt and lasting relief.

Case 2. Miss I. D., aged 35, was seen in a severe asthmatic state on September 2, 1933, having had perennial allergic asthma for 18 years. The patient had previously shown a marked sensitivity to the common pollens, epidermals and to a large number of foods. On checking the dermal tests a marked generalized reaction was encountered within one minute after the application of a drop of concentrated extract of short ragweed upon the scarified skin. According to the patient's statement a similar experience had occurred previously when she was given an injection of $\frac{1}{10}$ Noon unit (0.0001 mg.) of ragweed pollen intradermally. Being aware of this sensitivity we endeavored to produce frequent local wheals without injections, namely, by applying a drop of ragweed extract for a graduated period of time upon the scarified skin and washing it off at first after one second, then three seconds, then eight seconds, etc., at intervals of from one-half to two hours judging the time interval from the size of the local wheal produced. At the end of the second day the patient could tolerate the extract on the scarified skin for 20 minutes without producing a generalized reaction. A marked local edema had ensued after each application. On the third day it was possible to inject a dose of $\frac{1}{50}$ unit (0.00002 mg.) ragweed pollen; this was followed up at intervals of two hours by $\frac{1}{33}$ unit (0.00003 mg.), $\frac{1}{20}$ unit (0.00005 mg.), $\frac{8}{100}$ unit (0.00008 mg.). On the sixth day 150 units (.15 mg.) was reached. Upon the second application of the extract to the skin the asthmatic condition distinctly improved. Soon after the first intradermal injection the patient became free from asthma with the exception of slight attacks at night, which subsided entirely after two more days, in spite of the fact that the ragweed pollen season had not yet been terminated.

Comment: In this case an unusually marked degree of sensitivity was combated by rapid hyposensitization treatment. The production of local wheals either by scratch or subcutaneous application of the antigen must have been instrumental in bringing about prompt relief. While unquestionably various other antigens were contributing to this patient's asthmatic condition, the control of what appeared to be the principal reactor at that time, we believe, aborted the attack.

Case 3. Miss T. F., 52 years old, had had severe attacks of asthma during the past 10 years lasting as a rule from late May to the middle of October. Two sisters had also been suffering from allergic asthma. On skin testing positive reactions to the grass pollens, the ragweeds, orris root, wheat and egg were obtained. Admitted to the Charles Goodwin Jennings Hospital on August 11, 1936, with severe asthma, she was treated with a combination of antigenic extracts 1 to 4 units (0.001 to 0.004 mg.) of pollen in conjunction with epinephrine, ephedrine, barbiturates. The condition became progressively worse. In addition to 4 to 6 daily doses of epinephrine, opiates, calcium, iodides, oxygen and glucose intravenously were resorted to. On the fourth day of admission when the patient was seen by one of us (G. L. W.) all medication was discontinued except for $\frac{1}{10}$ or $\frac{2}{10}$ c.c., of 1:1000 epinephrine given

about two to four times in 24 hours. This resulted in no change of the severe asthmatic state. The following morning the patient was placed on a rapid hyposensitization régime starting with an initial dose of ⅒ unit (0.0001 mg.) of pollen extract with a very slight increase of doses at hourly intervals. The first five injections did not cause local swelling. When a slight wheal was obtained with the sixth dose, 2 units (0.002 mg.), a decided improvement was noted. However, the asthma did not completely subside. For the following injections another extract was employed with which no more wheals were obtained in spite of a rather marked increase in doses. (It was determined later that this extract had not been made up in the usual manner and was of very little potency.) The asthma recurred and became gradually worse until the patient again was in a critical condition. An intramuscular injection of 50 c.c., of serum from a patient recovered from pollen asthma was of no avail. Assuming that the lack of response to the treatment might be due to the insufficient potency of the extract it was replaced, without the patient's knowledge, by the one previously used. The initial dose ⅒ of 1 unit (0.0001 mg.) produced a wheal of about 2½ cm. in diameter with pseudopods. Relief was noted after 20 minutes. Subsequent treatments were given at intervals of one to three hours. Although the doses were increased only very slightly, local reactions occurred after each injection. On August 23 a dose of 80 units (0.8 mg.) was reached. The patient was discharged from the hospital a few days afterwards.

Comment: This represents another patient with severe asthma in a critical state in whom various therapeutic measures had failed. Here again, the improvement coincided with the production of local reactions by the antigen. The failure to elicit such reactions apparently resulted in a relapse. An impotent extract accounted for this fact. It is noteworthy that the dose of 0.1 unit failed at first to elicit a local reaction while after four days, it resulted in definite wheals.

Conclusions

1. Rapid hyposensitization, we believe, deserves a definite place in the treatment of allergic diseases. Particularly in the severe asthmatic in whom the causative antigens are known, it has proved to us to be the method of choice.

2. Successful treatment by this method is dependent on the administration of the proper antigen or combination of antigens, i.e., those which form the patient's dominant sensitivity.

3. The danger of causing constitutional reactions or of aggravating existing symptoms can be obviated if one abides by the following principles:

a. The initial dose should be sufficiently low so as not to produce much local swelling.

b. The doses and intervals between treatments should be carefully gauged for each individual injection, the principal guide being the degree of local edema which is produced by the previous one.

c. An incipient constitutional reaction which may merely manifest itself by a temporary aggravation of existing symptoms should be recognized and carefully guarded against by a readjustment of the proposed schedule of treatment.

d. No epinephrine, or as little as possible, should be used in conjunction with the treatment in order not to interfere with the production of a local swelling.

BIBLIOGRAPHY

1. BESREDKA, A.: De la vaccination anti-anaphylactique, Compt. rend. Soc. de biol., 1908, lxv, 479.
2. FREEMAN, J.: "Rush" inoculation, Lancet, 1930, i, 744.
3. TUFT, L.: Fatalities following the reinjection of foreign serum, Am. Jr. Med. Sci., 1928, clxxv, 325.
   BLANKENHORN, M. A.: Anaphylactic shock and failure of desensitization, Jr. Am. Med. Assoc., 1925, lxxxv, 325.
4. WALDBOTT, G. L., and ASCHER, M. S.: Rapid hyposensitization, Jr. Allergy, 1934, vi, 93.
5. VAUGHAN, W. T.: An improved co-seasonal treatment, Jr. Allergy, 1932, iii, 542.
   PHILLIPS, E. W.: Intradermal pollen therapy during the attack, Jr. Allergy, 1933, v, 29.
6. WALDBOTT, G. L., and ASCHER, M. S.: The rôle of accidental puncture of veins in the production of allergic shock, ANN. INT. MED., 1936, ix, 1232–1239.
7. RACKEMANN, F. M., and WAGNER, H. C.: Specific desensitization of skin sites in actively sensitive persons, Jr. Allergy, 1936, vii, 542–551.

THE THERAPEUTIC USE OF VENESECTION IN POLYCYTHEMIA *

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Although venesection has been used for many years as an emergency measure in erythremia, its general use as a therapeutic agent in this disease has been considered contraindicated on the grounds that reduction of the blood level by this means would act as a further stimulus to erythrocyte production.[1] Recent investigations, however, have indicated that this assumption may be unwarranted. Falconer [2] has shown that the repeated removal of from 200 to 600 c.c. of blood at intervals of from a few days to three weeks did not increase the reticulocyte percentage above normal limits. Reimann and Breuer [3] have studied the effects of systematic venesection in seven patients with polycythemia vera. Reduction in the red blood cell and hemoglobin level was accomplished by repeated bleeding over a period of several weeks. The resulting symptomatic and hematologic remissions were maintained for an average period of two years without further treatment. Detailed studies of the effect of venesection on the various other hematologic and circulatory abnormalities characteristically found in polycythemia have not been encountered in the literature.

This communication reports the results of a study of the therapeutic effect of venesection in the treatment of five cases of erythremia in whom the use of phenylhydrazine was considered inadvisable because of age or a history of previous vascular thrombosis.[4] In addition to clinical observations and determination of the red blood cell and hemoglobin levels and the reticulocyte percentage, studies of the hematocrit, blood volume, blood viscosity and, in some instances, circulation time and oxygen saturation of the arterial blood were made before, during and after periods of bleeding. Two (R. R. and A. G.) of the five patients studied presented the characteristic picture of polycythemia vera, without demonstrable cause for the high hemoglobin and red blood cell levels. Patients M. M. and M. P. have also been considered instances of polycythemia vera, although cardiac lesions, which may have led to some degree of anoxemia, were demonstrable; both exhibited splenomegaly and increased blood volume, usually not observed in the "secondary" types of polycythemia. The polycythemia of patient S. W. was apparently secondary to pulmonary fibrosis.

Methods

Venesection was accomplished either by the multiple syringe method or by the withdrawal of blood through a large needle into a flask under negative

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From the University of Rochester School of Medicine and Dentistry and the Medical Clinics of the Strong Memorial and Rochester Municipal Hospitals, Rochester, New York.

pressure induced by suction. As a rule, 500 c.c. of blood were withdrawn at intervals of from one to three days until the desired red blood cell, hemoglobin or hematocrit level was reached. In general, an attempt was made to reduce the hematocrit to a normal or slightly subnormal value. Red blood cell and white blood cell counts were estimated with the use of pipettes and counting chambers certified by the U. S. Bureau of Standards. For each red blood cell determination the average of two counts made in the usual manner was taken. Hemoglobin values were estimated in the Sahli hemoglobinometer, frequently calibrated by oxygen capacity. Reticulocyte counts

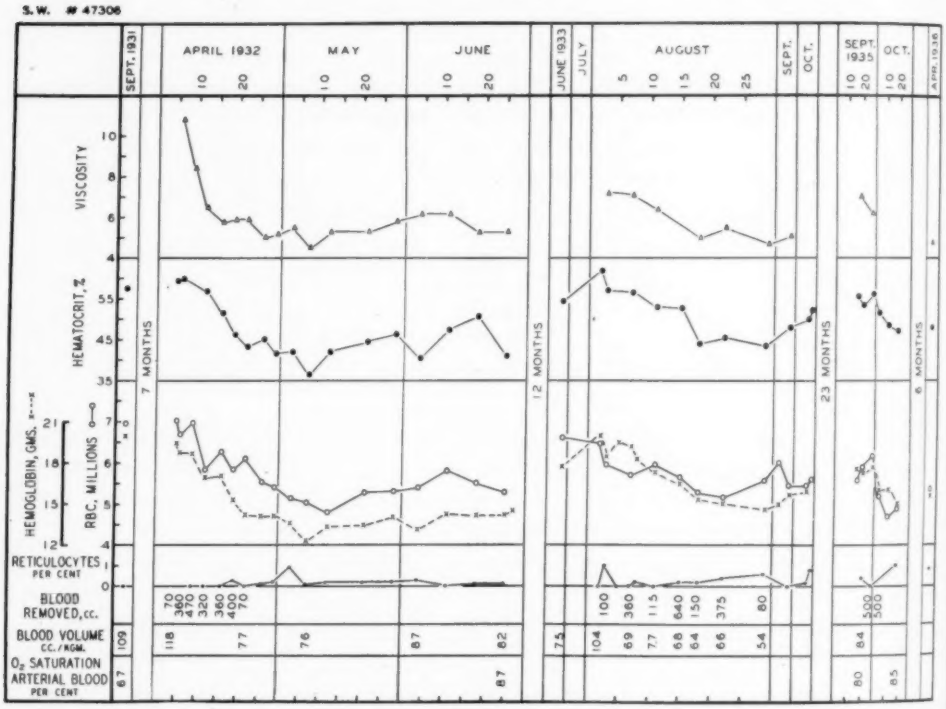

FIG. 1.

were made in " wet " preparations, stained with cresyl blue; 1,000 cells were counted for each determination. The relative volume of the red blood cells was determined by the Wintrobe hematocrit method.[5] Blood viscosity was determined by means of the Hess viscosimeter at room temperature. Blood velocity was determined as the arm to tongue circulation time by the Decholin method.* The blood volume was estimated by the method of Keith, Rowntree and Geraghty,[6] as modified by Hooper, Smith, Belt and Whipple.[7] We have some doubt as to whether the values obtained for blood volume in the presence of a high hematocrit value represent a close approximation of the actual volume of circulating blood when determined by this method. There

* The decholin-sodium used in these experiments was generously supplied by the Riedel de Haen, Inc.

is reason to believe that complete mixing of the dye may not occur in the time interval allowed to elapse between the injection of the dye and removal of the sample for determination of the dye content of the plasma, because of the marked increase of the blood viscosity and slowing of blood flow. The values obtained are probably lower than the actual blood volume. Although there may be some doubt as to the reliability of the absolute values

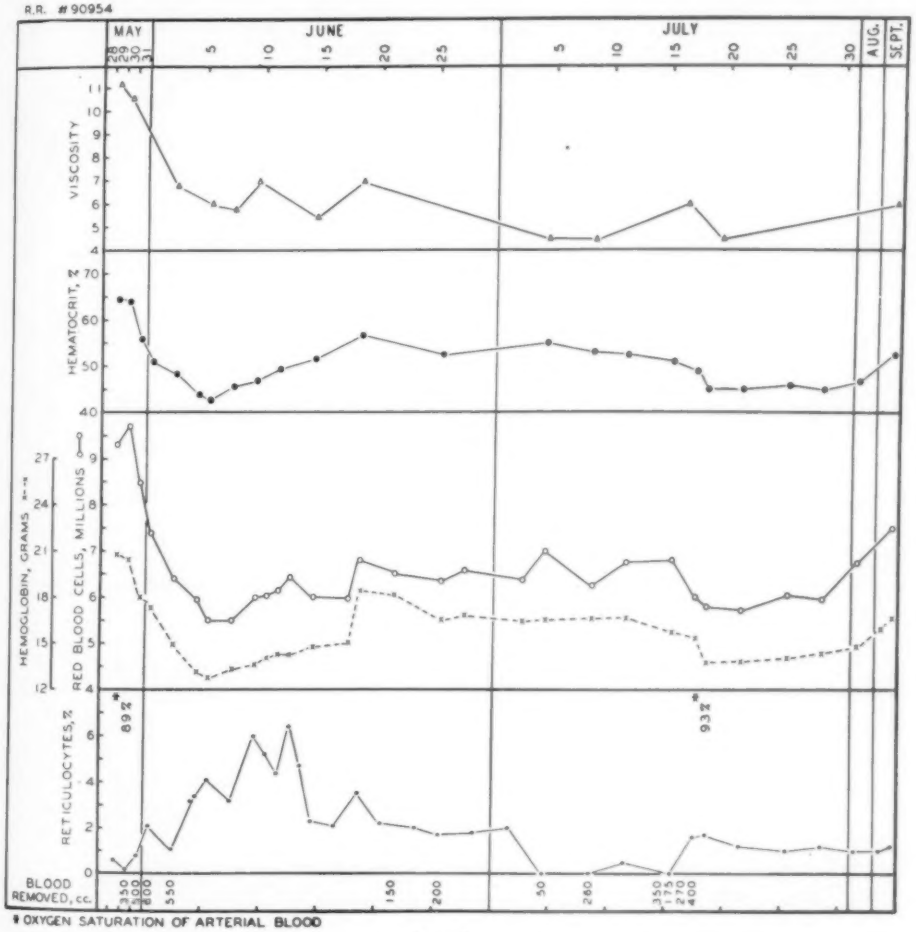

FIG. 2.

obtained in the presence of a high hematocrit and increased blood viscosity, a comparison of the effect of therapy on the blood volume estimations is of interest and some significance.

The following case reports are supplemented by summaries of hematologic observations presented in figures 1 to 4 and table 1. Some of the earlier observations in case 1 were made by Drs. S. H. Bassett and A. Hurtado in connection with studies of the iron balance.

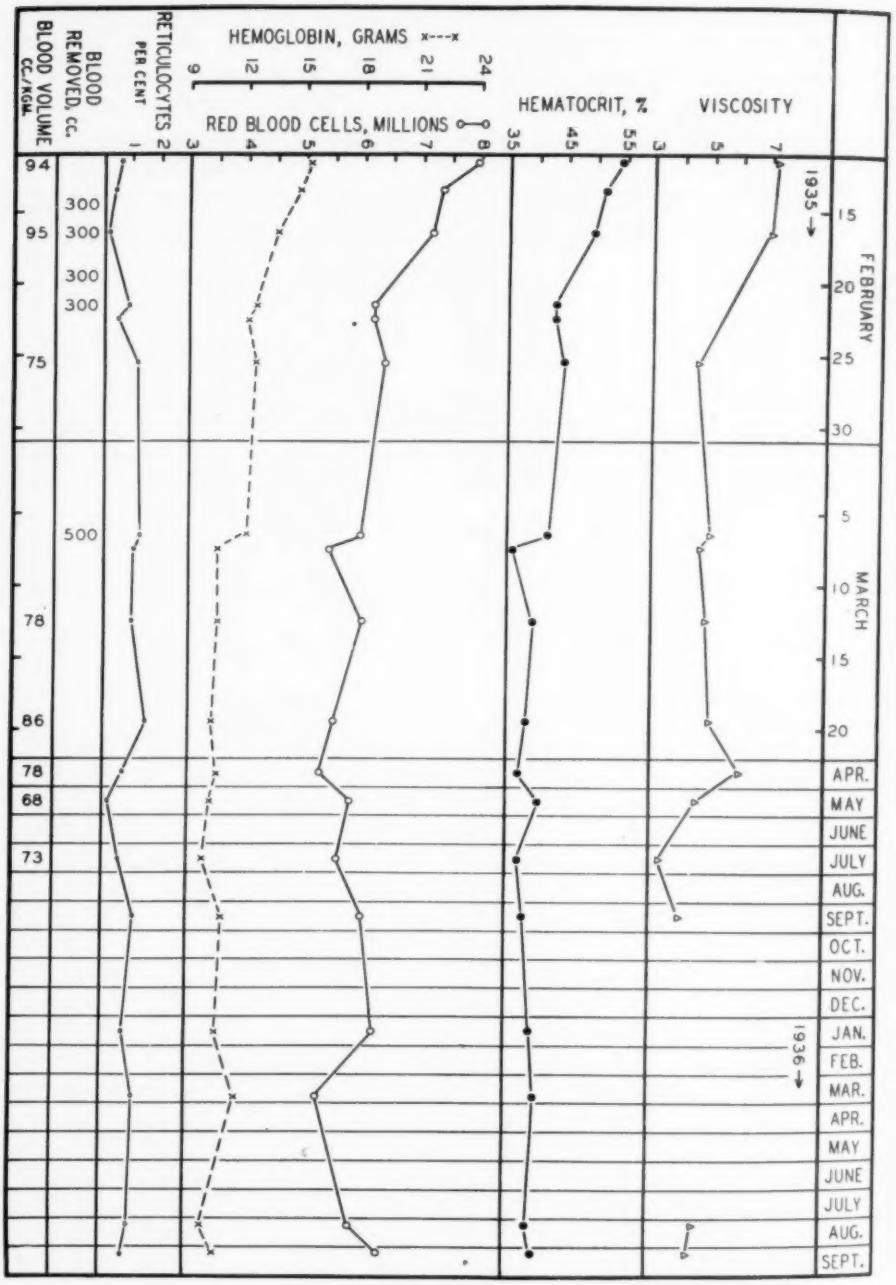
M.P. #92221
BLOOD VOLUME CC./KGM.
BLOOD REMOVED, CC.
RETICULOCYTES PER CENT
HEMOGLOBIN, GRAMS
RED BLOOD CELLS, MILLIONS
HEMATOCRIT, %
VISCOSITY
1935
1936
FEBRUARY
MARCH
APR.
MAY
JUNE
JULY
AUG.
SEPT.
OCT.
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FIG. 3.

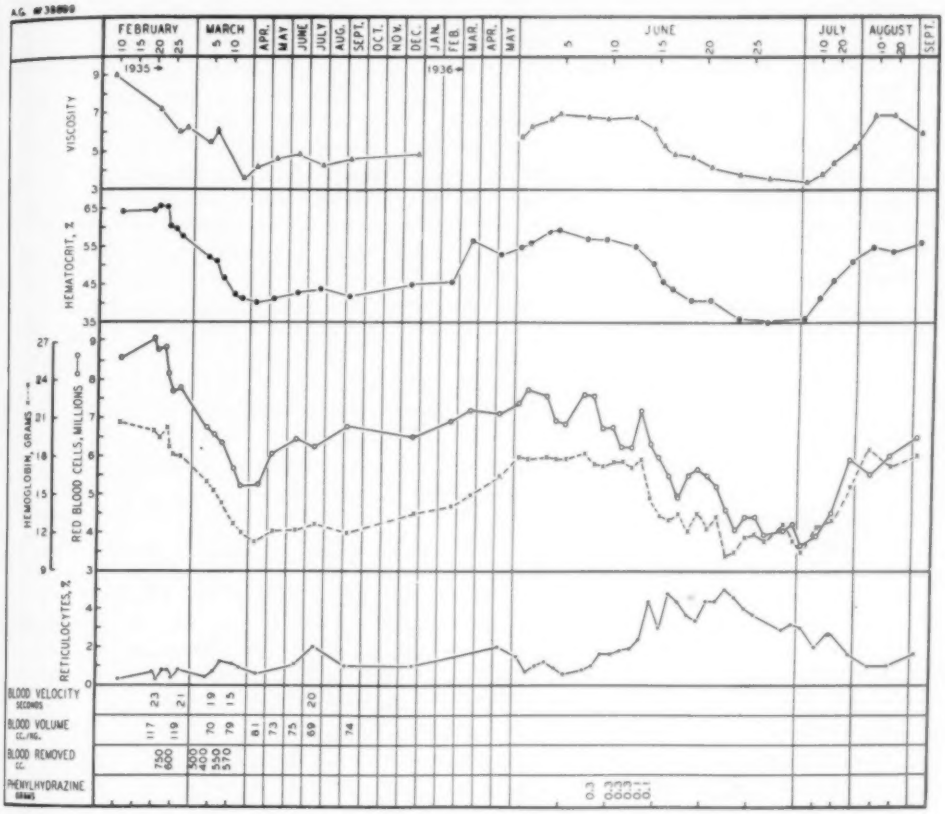

FIG. 4.

TABLE I

Subject	Date	R. B. C. Millions	Hgb. Grams	Hematocrit Per cent	Mean Corpuscular Volume Cubic Microns	Mean Corpuscular Hemoglobin $\gamma\gamma$	Remarks
A.G.	2–20–35	9.08	19.8	64.8	71.4	21.6	Before venesection.
	3–11–35	5.68	12.0	42.5	74.6	21.1	After venesection
	12–28–35	6.53	13.5	45.0	68.6	20.6	9 months after venesection
	6– 2–36	7.74	17.9	56.0	72.4	23.1	15 months after venesection
	7– 2–36	3.66	10.5	36.0	98.2	28.2	2 weeks after phenylhydrazine
	8–18–36	6.07	17.3	54.0	89.0	28.5	8 weeks after phenylhydrazine
M. M.	4– 1–33	7.08	19.9	66.0	93.2	26.2	Before treatment
	4–30–33	4.77	12.2	40.0	84.0	25.6	2 weeks after phenylhydrazine
	9–22–33	6.80	18.9	61.0	88.4	27.8	4 months after phenylhydrazine
	10– 3–33	6.15	15.7	53.0	86.6	25.2	After venesection
	12– 5–33	5.96	15.0	50.7	85.1	25.2	After venesection
	1–29–35	5.82	18.6	60.5	104.0	32.0	After phenylhydrazine for one year
	10–15–35	4.94	12.3	41.0	83.0	24.9	1 month after venesection
	5–26–36	5.60	15.5	45.0	80.3	27.7	8 months after venesection

Case Reports

Case 1. S. W., a 56 year old foundry worker, was admitted to the hospital on May 12, 1931 complaining of shortness of breath, "purplish color of the skin" and smothering sensation under the sternum of one year's duration. About six weeks before admission these symptoms became more intense. On admission the patient was orthopneic, and the respirations and pulse were rapid. The mucous membranes and nail beds were deeply cyanosed. The retinal veins were engorged and the neck veins greatly distended. Moderately coarse râles were scattered throughout the entire chest. The heart was markedly enlarged to the left. The liver was enlarged, but the spleen was not felt. There was pitting edema over the lower extremities.

The blood findings were as follows: red blood cells 7,300,000 per cu. mm.; hemoglobin 19.5 grams per 100 c.c., hematocrit 67.7 per cent and white blood cells 11,600 per cu. mm. The electrocardiograph showed right axis deviation. Roentgenogram of the chest revealed the heart to be greatly increased in all of its diameters. The pulmonary fields showed diffuse, fine reticular fibrosis, in addition to soft mottling and feathering over the lower fields. The vital capacity was 650 c.c.

The patient was treated by venesection (1,000 c.c.) and oxygen inhalation and on discharge one month later was much improved.

The patient was next seen in September 1931 and April 1932, at which time he was again dyspneic and orthopneic at rest. The pertinent findings in reference to the blood are shown in figure 1. With the removal of a total of 2,100 c.c. of blood, the red blood cell count, hemoglobin, hematocrit, blood volume and viscosity fell to slightly below the average values for normal individuals. There was no appreciable increase in the reticulocyte percentage. The oxygen saturation of the arterial blood rose from 67 to 87 per cent. When the patient was discharged from the hospital on June 27, 1932, his cardiac compensation was good for moderate activity and dyspnea was considerably ameliorated.

Twelve months later, the patient was again seen because of recent increase in dyspnea. The blood findings are given in figure 1 and show that there was again a marked increase in the red blood cell and hemoglobin level. After a series of venesections the level was again reduced to the normal zone where it remained for approximately two years. It is significant that none of the periods of bleeding in this patient were followed by any increase in the reticulocytes.

Case 2. R. R., a 40 year old brewmaster, was seen in this clinic in June 1934, because of a hematoma of the left thigh which had appeared following a fall. At this time the spleen was not felt and the red blood cell and hemoglobin levels were within normal limits.

In May 1935, the patient was readmitted to the hospital because of inability to talk and use the right arm and leg. For several weeks his wife had noted that the face and hands were becoming increasingly red and dusky. Examination revealed a red discoloration of the skin, particularly noticeable on the face, neck, hands and mucous membranes. The retinal veins were engorged and there was a small retinal hemorrhage lateral to the left disc. The spleen was palpable two fingers-breadth below the costal margin. Neurological examination showed right facial weakness and complete paralysis of the right arm and leg. Details of the examination of the blood are given in figure 2. In addition to these, the white blood cell count was 36,400 per cu. mm. and the icterus index, 32.

During a period of 5 days a total of 2,000 c.c. of blood was removed by venesection. Immediately after venesection the serum proteins were decreased to 4.4 grams per cent. This period of venesection was followd by an increase in the reticulocyte to 6.3 per cent.

Six weeks later, because of an increase in the blood counts (figure 2), an addi-

tional 1,200 c.c. of blood were removed. This was followed by a maximum reticulocyte response of only 1.7 per cent.

After the patient was discharged in July 1935, approximately 3,000 c.c. of blood were removed over a period of a year. There has been partial improvement in the paralysis and dysarthria and he has remained free of further symptoms referable to polycythemia. The spleen has not been palpable during the past year. Blood studies obtained in October 1936 through the courtesy of the patient's physician, Dr. C. B. F. Gibbs, were as follows: Red blood cells 6,130,000; hemoglobin 9.2 grams per 100 c.c.; hematocrit 31 per cent; reticulocytes 0.8 per cent; white blood cells 16,600; icterus index 8 and blood viscosity 3.6. From July 1935 to October 1936 the mean corpuscular volume fell from 76 to 51 cubic microns and the mean corpuscular hemoglobin from 24 to 15 micromicrograms.

Case 3. M. P., a 56 year old housewife, complained of dull aching pain in the left upper abdomen of two years' duration. During the past several months she had noted progressive enlargement of a mass in the left upper abdomen. In addition there had been dizziness and faintness occurring frequently during the past few months and sensations of burning of the feet. There had been several recent epistaxes. In childhood she had had rheumatic fever and since the age of 25, until the past two years, she had had seasonal hay fever and asthma, occurring in the autumn. At the age of 50, she had experienced an episode of severe precordial pain, accompanied by prostration and collapse. Since that time she had taken digitalis regularly.

In February 1935 physical examination showed a dusky violaceous discoloration of the face, neck and hands. The mucous membranes were deep red in color. The retinal veins were engorged. The heart was enlarged to the left and to the right, the pulmonary second sound was accentuated. A loud, rough, systolic murmur was transmitted from the apical region to the axilla. The spleen was markedly enlarged, extending downward to the iliac crest. The liver edge was palpable three fingersbreadth below the costal margin.

The blood findings are given in detail in figure 3. Other pertinent findings were: White blood cells 14,100 per cu. mm. with a normal differential count; mean corpuscular volume 69 cubic microns; mean corpuscular hemoglobin 19 micromicrograms. Electrocardiographic tracing showed right axis deviation. Roentgenogram of the chest showed increased linear markings with fine feathering of both pulmonary fields. The heart was enlarged in all of its diameters.

Between February 15 and March 7 a total of 1,700 c.c. of blood was removed by venesection. Reduction of the red blood cell count was followed by symptomatic improvement and a slight reduction in the mean corpuscular volume and hemoglobin and in the size of the spleen. During and after the period of bleeding there was no significant change in the white blood cell count or the differential count.

After discharge from the hospital digitalis was continued in maintenance dosage. Up to the present time, 20 months after venesection, there has been no significant change in the blood picture and there have been no symptoms referable to polycythemia. The spleen has remained at about the same size as when discharged from the hospital. Following venesection, this patient has maintained a mild degree of hypochromic, microcytic anemia without symptoms and without evidence of hemolysis or of excess red blood cell regeneration.

Case 4. A. G., a 55 year old housewife, was first seen in this clinic in 1930 at which time a diagnosis of duodenal ulcer was made. Examination of the blood showed no abnormalities at that time. The red blood cell count was 5,500,000 per cu. mm., hemoglobin 14.2 grams per 100 c.c.

The patient was admitted to the hospital in February 1935, complaining of frequent dizzy spells and increased color of the face and hands of several months' duration. On examination deep red color of the face and hands was noted. The retinal

veins were dilated. The heart and lungs were negative. The lower border of the spleen was felt five fingers-breadth below the costal margin. The liver edge was at the costal margin. The left foot and the lower left leg were cyanotic and swollen, apparently due to thrombosis of the deep veins of the leg.

Laboratory data in addition to those charted in figure 4 revealed an oxygen saturation of the arterial blood of 94 per cent; icterus index of 8, and a white blood cell count of 9,800 per cu. mm. with a normal differential count. Roentgenogram of the chest showed no pulmonary or cardiac abnormalities.

During a period of 14 days a total of 3,370 c.c. of blood was removed by repeated venesection. The maximum reticulocyte count during and after the period of bleeding was 1.2 per cent. At the time of discharge from the hospital the abdominal symptoms, the dizziness, faintness and the pain in the left foot had disappeared. The spleen decreased in size so that it was no longer palpable.

The patient was observed at intervals in the Out-Patient Department. The symptomatic and hematologic remission induced by venesection continued for approximately one year. In February 1936 occasional dizziness was experienced; during the next four months the frequency of the attacks increased and there was a gradual rise in the number of red blood cells. The spleen again became palpable two fingers-breadth below the costal margin. In June 1936 it was decided to observe the effect of a course of phenylhydrazine for comparison with the effect of venesection. During the period of hemolysis the reticulocytes increased to 4.8 per cent, mild jaundice appeared and was accompanied by an increase in the icterus index to 30. During the period of blood destruction the serum proteins increased from 6.3 to 7.2 grams per cent and the white blood cell count from 6,450 to 21,100 per cu. mm. with some increase in the percentage of neutrophiles; no immature white or red blood cells appeared in the peripheral blood. The white blood cell count and differential count, the icterus index and the serum protein returned to pre-treatment levels within three weeks after discontinuance of the administration of the drug. The dizziness disappeared with the reduction in the blood level, but there was no significant change in the size of the spleen. Within two months the red blood cell count had risen to the pre-treatment level (figure 4) and symptoms had returned. A second course of treatment with this drug was given with similar results. In this patient the administration of phenylhydrazine was accompanied on both occasions by marked increase in ulcer symptoms, so that she refused to take a maintenance dose of the drug.

Case 5. M. M., a 40 year old stenographer, was admitted to the hospital in April 1933 complaining of fainting and dizzy spells of six years' duration. Her complexion had always been ruddy, but during recent years the bluish red color of her face, neck and hands had increased. There was a history of frequent epistaxes. In childhood she had had scarlet fever, chorea and poliomyelitis. At the age of 24 right salpingectomy and oöphorectomy was done and at 27 she had peritonitis following an abortion. At 34 thyroidectomy was performed.

Physical examination showed bright, bluish red color of the face, neck, upper chest, hands and legs. There was slight exophthalmos and the retinal veins were engorged. The area of cardiac dullness was enlarged to the left; there was a presystolic thrill at the apical area, with systolic and presystolic murmurs. Blood pressure 160 systolic, 100 diastolic. The spleen was palpable three fingers-breadth below the left costal margin.

The hematologic picture is shown in table 1. The white blood cell count was 7,900 per cu. mm. Differential count was as follows: neutrophiles 58 per cent; lymphocytes 24 per cent; monocytes 5 per cent; eosinophiles 10 per cent and basophiles 3 per cent. Roentgenogram of the chest showed prominent linear pulmonary markings and cardiac enlargement. The electrocardiogram was normal.

During a period of 14 days, the patient received a total of 1.8 grams of phenyl-

hydrazine hydrochloride. Two weeks later the blood level was slightly below normal (table 1). The viscosity of the blood fell from 15 to 6 and the blood volume from 91 c.c. to 72 c.c. per kilogram of body weight. Following the administration of the drug the symptoms were ameliorated. Within two months, in spite of the administration of small doses of the drug, the symptoms began to increase and the blood level began to rise.

She was readmitted to the hospital in September 1933 because of a convulsive seizure. The blood viscosity was 17. During a period of two months 2,000 c.c. of blood were removed by six venesections. The maximum reticulocyte response during this period was 2.0 per cent.

In February 1934 the red blood cell count was again elevated and phenylhydrazine (1.0 gram) was again given. This course of the drug was followed by thrombosis of the left dorsalis pedis artery. During the following 18 months the patient was followed at frequent intervals in the Out-Patient Department, receiving a total of 7.6 grams of phenylhydrazine in doses varying from 0.1 to 0.3 gram per week. During this time there was progressive increase in the hemoglobin, hematocrit, viscosity and the mean corpuscular volume, although there was little change in the number of red blood cells (see table 1 under date 1/29/35). At this time the patient was having frequent fainting episodes and complained of tingling of the fingers. In March 1935 after an epistaxis, which resulted in the loss of an estimated pint of blood, these symptoms became less severe.

In April 1935 the removal of 1,500 c.c. of blood resulted in a hematologic remission of four months' duration. It is of interest that on this occasion venesection was followed by an increase in the reticulocytes to 6.2 per cent. In September 1935 the erythrocyte count had increased to such a level that 1,500 c.c. of blood were removed, again resulting in a decrease in the blood level to slightly less than normal (table 1). The maximum reticulocyte response following venesection on this occasion was only 2.0 per cent. During the following eight months there was a slight rise in the red blood cell and hemoglobin values.

In this patient there was only partial correlation between the blood level and the presence of fainting episodes, which were in many ways suggestive of petit mal seizures. The changes in the size and hemoglobin content of the red blood cells following the use of venesection and phenylhydrazine were of particular interest and will be discussed.

Results

By means of repeated and systematic venesection at intervals of from one to several days it was possible to reduce the relative volume of the red blood cells to a normal or slightly subnormal level. There was a corresponding decrease in red blood cells and hemoglobin and reduction in the blood viscosity, blood volume and blood velocity to approximately normal levels. In two subjects, the oxygen saturation of the arterial blood was increased following venesection. Hematologic improvement was usually accompanied by marked relief of symptoms referable to the polycythemia, and by reduction in the size of the spleen. The characteristic "red" cyanosis disappeared and there were evidences of improvement in the capillary and venous circulation as the blood level was lowered. The reticulocyte response to bleeding was of particular interest because of its significance as an index of erythropoietic activity. Nine of the eleven periods of bleeding were followed by no significant increase in the percentage of reticulocytes. It may

be of significance that the two periods of venesection which were followed by reticulocyte increases followed periods of blood destruction. In the case of patient M. M. the period of bleeding which was accompanied by a reticulocytosis of 6.2 per cent followed the prolonged administration of phenylhydrazine. Patient R. R., when first seen, was jaundiced, with an icterus index of 32, interpreted as evidence of previous blood destruction. Four of the five patients experienced symptomatic and hematologic remissions of from eight months' to two years' duration without further treatment. Remissions of shorter duration were observed only in those patients who exhibited a reticulocyte response to venesection and who presumably had abundant stores of iron and other blood-building materials as the result of previous blood destruction.

Unfavorable reactions to venesection were not encountered, even when large amounts of blood were withdrawn within a period of a few days. No evidences of stimulation of the white blood cell or platelet elements of the bone marrow were observed. A temporary decrease in the level of the serum proteins was noted for a few days after the withdrawal of large amounts of blood but no clinical manifestations of serum protein deficiency appeared.

In one patient detailed observations of the effect of both venesection and phenylhydrazine are available (patient A. G., figure 4). Satisfactory reduction in the red blood cells, hemoglobin, hematocrit and blood viscosity, and temporary relief of symptoms were accomplished by the administration of a relatively small dose of phenylhydrazine hydrochloride. In comparing the effect of the two therapeutic procedures in this patient, at least two significant and probably related observations are noteworthy. First, the administration of phenylhydrazine was followed by a reticulocytosis not observed after venesection. Second, the remission induced by phenylhydrazine was of less than two months' duration, as contrasted with a remission of 15 months' duration following venesection. As a result of the gastrointestinal symptoms which accompanied the administration of phenylhydrazine, this patient insists on returning to the use of venesection when further treatment of the polycythemia becomes necessary.

It is of interest that three of the five patients exhibited microcytosis and hypochromia of the red blood cells of significant grade. In two patients observations of the red blood cell size and hemoglobin content after treatment with both phenylhydrazine and venesection are available (table 1). In the case of patient A. G., there was no significant change in the microcytosis and hypochromia during the 15 months' remission which followed venesection. The administration of phenylhydrazine, however, was followed within a relatively short period of time, by a consistent and significant increase in the cell size and hemoglobin content. Patient M. M. originally presented red blood cells which were normal in size and hemoglobin content. No significant change was observed after a single course of phenylhydrazine,

followed by a period of venesection. The administration of phenylhydrazine in maintenance doses during a period of one year, however, resulted in a significant increase in the mean corpuscular volume and hemoglobin. Although the number of red blood cells per cubic millimeter showed but little change during this period, the increase in erythrocyte size was sufficient to result in a gradual increase in the hematocrit, hemoglobin and blood viscosity, with coincident increase in the severity of symptoms. The removal of a total of 3,000 c.c. of blood by repeated venesection was followed by a significant reduction in the cell size and hemoglobin content.

Discussion

The syndrome of erythremia is characterized by a marked hyperplasia of the bone marrow, as a result of which characteristic increases in the red blood cell count, hemoglobin, hematocrit, blood viscosity and blood volume occur. The symptoms of the disease result for the most part from the plethora and stasis of blood flow due to the marked increase in blood volume and the overfilling of the vascular tree, especially in the capillary bed. Splenomegaly is usually present. Phlebitis and vascular thromboses are common.

Although the primary lesion is in the bone marrow, there has been no unanimity of opinion as to the etiology of the pathologic increase in erythropoietic activity. There are those who have felt that the increased activity of the bone marrow is malignant in nature and analogous to the disordered cell activity which occurs in leukemia. Others have been impressed with the probable relationship of polycythemia to anoxemia, which is generally recognized as a powerful stimulant of erythropoietic activity. The "secondary" polycythemia observed in patients with cardiac and pulmonary lesions and the polycythemia encountered at high altitude would seem to be best explained on this basis. Further evidence of the probable importance of anoxemia has recently been provided by the studies of Reznikoff, Foot and Bethea.[8] These authors observed distinct capillary thickening and subintimal and adventitial fibrosis of subarteriolar capillaries, arterioles and arteries of the bone marrow of seven patients with polycythemia vera. They raise the question whether the anoxemic state caused by vascular disease in the bone marrow itself may be responsible for the excess red blood cell production, particularly in those patients without obvious lesions in other viscera which might lead to anoxemia. With such an explanation of the bone marrow overactivity in so-called polycythemia vera, the erythremia and symptomatology of both types of polycythemia may be reasonably regarded as an overcompensatory response of the bone marrow to lowered oxygen tension. Even in those types of polycythemia in which the increase in red blood cells seems to be in response to an increased demand for oxygen-carrying material, the circulatory disturbances resulting from the increased blood viscosity and slowing of the blood flow may increase the difficulty in

oxygen exchange. Under these circumstances the advantage gained by increase in hemoglobin may be more than offset by the disadvantage of circulatory embarrassment due to the increased corpuscular mass. In such instances of "secondary" polycythemia, as well as in polycythemia vera, symptomatic improvement follows relief of the circulatory embarrassment by reduction in the number of erythrocytes by means of appropriate therapeutic measures.

Of the various therapeutic procedures recommended for the treatment of erythremia, phenylhydrazine has been most extensively used and its effects most thoroughly studied. Satisfactory hematologic and symptomatic remissions have been induced by means of this agent in a large number of reported cases. Brown and Giffin [9] have shown that reduction in the red blood cell count and hemoglobin is accompanied by reduction in the hematocrit, blood viscosity and blood volume and by improvement in circulatory efficiency. Although the effect of a single course of phenylhydrazine is of relatively short duration, remissions may be prolonged by the continued administration of a suitable maintenance dose of the drug, the size of which must be individually determined. A number of patients have been described in whom satisfactory remissions have been maintained for periods of many years.[10] Although the large majority of patients with polycythemia apparently may be satisfactorily controlled by the use of phenylhydrazine preparations, the use of this drug has certain practical as well as theoretical disadvantages. The amount of the drug required to produce the desired effect varies widely from patient to patient. Due to its cumulative and delayed action, the degree of hemolysis produced may be difficult to predict and control. Instances of severe and even fatal anemia have been observed following its use in polycythemia. Giffin and Conner [4] state that it should be used with extreme caution, if at all, in elderly patients and in those in whom thromboses have been observed or suspected.

The effect of phenylhydrazine on the blood and the bone marrow has been extensively studied in the experimental animal as well as in the patient with polycythemia. Hemolysis is accompanied by the appearance of jaundice, increase in circulating bilirubin and increase in the urinary excretion of bile pigments and porphyrins. Blood destruction induced by phenylhydrazine, however, results in no increase in the excretion of iron, which is retained and stored in the various organs, particularly the spleen and liver.[11] It is apparent, therefore, that iron and perhaps other blood building materials, liberated by the hemolytic action of phenylhydrazine, are retained in the body for future use in erythropoiesis. The use of the drug in polycythemia is usually followed by a marked leukocytosis, frequently with the appearance of immature myeloid elements in the peripheral blood. Thrombocytosis also usually occurs and is thought to be responsible for the peripheral thromboses occasionally observed after the administration of phenylhydrazine. Observations in humans, as well as in animals, have shown that phenylhydrazine, either directly or indirectly through its hemolytic action, is

a powerful bone marrow stimulant, resulting in proliferation of erythroid, myeloid and platelet elements of the bone marrow. The reduction in the red blood cell count is usually accompanied by reticulocytosis, leukocytosis and thrombocytosis, interpreted as evidence of increased bone marrow activity. The administration of phenylhydrazine to animals may be followed by the appearance of nucleated erythrocytes and immature myeloid cells in the spleen, liver and other organs.[12] Harrop [1] has suggested that intensive treatment with phenylhydrazine, radiation or venesection may be responsible for the leukemoid changes observed in some cases of polycythemia. It appears that, although phenylhydrazine, due to its hemolytic action, is capable of controlling the symptoms and peripheral blood picture of erythremia, its effect on the bone marrow may accentuate the existing marrow hyperplasia and may lead, through continued stimulation, to the appearance of leukemoid changes simulating myeloid leukemia.

Although there is a considerable literature dealing with the use of roentgen therapy in polycythemia, the effects of its use in this disease have not been extensively studied. Symptomatic improvement and reduction in the red blood cell and hemoglobin levels may follow irradiation of the spleen or long bones. Some students of the disease feel that roentgen therapy is the safest and most effective form of therapy available.[1]

Recent reports have suggested the use of solution of potassium arsenite [1c] and repeated aspiration of the gastric contents [13] in the treatment of polycythemia. The usefulness of these measures remains to be determined.

Objections to the general use of venesection in the treatment of polycythemia have been limited almost entirely to the assertion that it would result in increased stimulation of an already active bone marrow. This statement is apparently based primarily on observations of the results of hemorrhage in individuals with previously normal blood levels and on the result of bleeding experiments in animals. The degree of bone marrow stimulation observed under such conditions, however, appears to depend on several factors. Among these are the amount of blood lost, the resulting degree of anemia and the availability of iron and other blood building materials. The removal of as much as 500 c.c. of blood from a normal individual is followed by no reticulocyte response. However, the anemia occurring in humans after a large hemorrhage is followed by reticulocytosis and rapid regeneration of blood, provided adequate stores of iron and other blood building materials are available. It is significant that in those patients whose iron stores have been depleted by means of chronic blood loss, reticulocytosis and other evidences of blood regeneration do not appear until adequate amounts of iron are provided.[14] Direct evidence that blood withdrawal results in increased bone marrow activity in erythremia is apparently limited to occasional observations of rapid red blood cell regeneration after reduction to anemic levels following a large hemorrhage. Our observations, as well as those of Falconer [2] and of Reimann and Breuer [3] indicate that, in polycythemia, the use of venesection under controlled conditions is

not ordinarily accompanied by evidences of increased bone marrow activity. In this regard, it should be noted that only a slight, if any, degree of anemia is produced and that the withdrawal of the large amounts of blood necessary to reduce the hematocrit to a normal or slightly subnormal level results in the removal from the body of relatively large amounts of iron and other blood building materials. The prolonged remissions which follow reduction of the blood level by this means and the absence of reticulocyte response are interpreted as evidence that bleeding under these conditions may not result in significant increase in erythropoietic activity.

Venesection is a relatively simple procedure, the effects of which may be accurately controlled. Its use is apparently not attended by many of the dangers and undesirable side effects of phenylhydrazine and roentgen therapy. Its advantages and relative freedom of disadvantages would appear to warrant its more extensive use in the treatment of polycythemia, particularly, for the present at least, in those patients in whom the more orthodox therapeutic measures seem to be contraindicated or inadvisable.

A consideration of the erythrocyte characteristics in polycythemia, particularly in relation to the iron metabolism and the effect of therapeutic procedures is of interest. Hurtado [15] noted that the polycythemia observed in natives living at high altitudes was characterized by a red blood cell which was larger, contained less hemoglobin and was less saturated with oxygen than the erythrocyte of normal subjects living at sea level. A marked increase in the hematocrit was observed, although the average number of grams of hemoglobin per 100 c.c. of blood had approximately the same value as the normal average at sea level. The corpuscular volume and the corpuscular hemoglobin varied inversely with the level of the red cell count, so that the hemoglobin concentration was found to be remarkably constant at approximately 25 per cent, considerably below the average normal of 34 per cent at sea level. These observations suggested that the adaptation processes to high altitude, from the point of view of blood morphology, were to be found not primarily in red cell and hemoglobin increases but rather in a close correlation between the cell number, volume and hemoglobin content and in the existence of a larger surface area in a given volume of blood and in the individual erythrocyte for the hemoglobin and oxygen content.

Similar studies of erythrocyte characteristics apparently have not been made in other types of polycythemia. It is usually stated that the size and diameter of the erythrocytes in polycythemia are normal,[1a] although the color index is nearly always decreased. In three of the five patients here reported, the mean corpuscular volume and hemoglobin content were well below the lower limits of normal and in one of these (R. R.) were further decreased after repeated venesection. In two instances (table 1) the cell size and hemoglobin content increased after the administration of phenylhydrazine, decreased following venesection. The microcytosis and hypochromia observed in these patients were similar to the changes which take

place in the erythrocytes in the iron deficiency anemias, suggesting that in at least some patients with polycythemia a relative iron deficiency may result from the increased demand for blood-building materials.

A decrease in the average volume of the red blood cells in polycythemia should be physiologically advantageous, since the increased blood volume and blood viscosity, which are responsible for the stasis and slowing of blood flow, are due to the elevated hematocrit. The level of the latter is determined not only by the number of red blood cells per cu. mm. but also to a large extent by the mean corpuscular volume. Recent studies of the anemias [16] have indicated that the size, volume and hemoglobin content of the erythrocytes are determined by the relative amounts of stroma and hemoglobin-building substances, particularly iron, which are available. If it may be assumed that, in the presence of adequate stroma-building material, the level of erythrocyte production in polycythemia is determined by the stimulating effect of anoxemia, then the size of the red blood cells delivered to the peripheral circulation should depend on the amount of iron available for hemoglobin construction. A comparison of the effects of phenylhydrazine and venesection appears to support this hypothesis. It has already been noted that the large amounts of iron resulting from hemolysis induced by phenylhydrazine, are stored in the body for future use. The therapeutic use of venesection, on the other hand, removes from the body large amounts of iron and other erythrocyte building-materials, which are then no longer available for the resynthesis of hemoglobin. Reimann and Breuer [3] stressed the apparent importance of this factor and felt that it was chiefly responsible for the good results observed in their patients. It is of interest that in five of their seven cases the color index was decreased after venesection.

The observations in patient R. R. indicate that the repeated withdrawal of large amounts of blood may, in time, result in a blood picture similar to that observed in chlorosis and in the iron deficiency anemias. Such an occurrence should not be considered a contraindication to the therapeutic use of venesection for the control of the polycythemic state. If considered advisable, the cell size and hemoglobin content may be increased by the administration of suitable amounts of iron.

Summary

The therapeutic use of venesection has been studied in five patients with polycythemia.

Reduction of the elevated hematocrit values to a normal or slightly subnormal level by means of systematic venesection was accompanied by comparable reduction in red blood cells, hemoglobin, blood viscosity and blood volume and by improvement in circulatory efficiency. The symptomatic and hematologic remissions so induced were maintained for relatively long periods without further treatment. Venesection was followed by increases in the reticulocyte percentage only in those instances in which the tissue

stores of iron were presumably increased as a result of previous blood destruction.

The prolonged remissions and absence of reticulocyte increases following reduction of the blood level indicate that venesection under these conditions does not result in significant increase in erythropoietic activity. The relatively long duration of the symptomatic and hematologic remissions observed after venesection is thought to be due to the fact that removal of the large amounts of blood required to produce the desired effect results in the loss from the body of considerable amounts of iron and other potential blood building materials. In several instances decrease in erythrocyte size and hemoglobin content was observed after periods of bleeding.

Systematic venesection appears to be a relatively safe and efficient therapeutic procedure, which compares favorably with other measures used in the treatment of polycythemia.

BIBLIOGRAPHY

1. (*a*) HARROP, G. A.: Polycythemia, Medicine, 1928, vii, 291.
   (*b*) PARK, G. T., and CRAVER, L. F.: The radiation therapy of polycythemia vera, Am. Jr. Med. Sci., 1930, clxxx, 609.
   (*c*) FORKNER, C. E., SCOTT, T. F., and WU, S. C.: Treatment of polycythemia vera with solution of potassium arsenite, Arch. Int. Med., 1933, li, 616.
2. FALCONER, E. H.: Treatment of polycythemia. The reticulocyte response to venesection, phenylhydrazine and radiation, ANN. INT. MED., 1933, vii, 172.
3. REIMANN, F., and BREUER, A.: Die Aderlassbehandlung der Erythrämie, Ztschr. f. klin. Med., 1935, cxxviii, 238.
4. GIFFIN, H. Z., and CONNER, H. M.: The untoward effects of treatment by phenylhydrazine hydrochloride, Jr. Am. Med. Assoc., 1929, xcii, 1505.
5. WINTROBE, M. M.: The size and hemoglobin content of the erythrocyte, Jr. Lab. and Clin. Med., 1932, xvii, 899.
6. KEITH, N. M., ROWNTREE, L. G., and GERAGHTY, J. T.: A method for the determination of plasma and blood volume, Arch. Int. Med., 1915, xvi, 547.
7. HOOPER, C. W., SMITH, H. P., BELT, A. E., and WHIPPLE, G. H.: Blood volume studies. Experimental control of a dye blood volume method, Am. Jr. Physiol., 1920, li, 205.
8. REZNIKOFF, P., FOOT, N. C., and BETHEA, J. M.: Etiologic and pathologic factors in polycythemia vera, Am. Jr. Med. Sci., 1935, clxxxix, 753.
9. BROWN, G. E., and GIFFIN, H. Z.: The treatment of polycythemia vera with phenylhydrazine, Arch. Int. Med., 1926, xxxviii, 321.
10. (*a*) STEALY, C. L.: Polycythemia vera. Report of a case treated with phenylhydrazine hydrochloride for seven and a half years, Jr. Am. Med. Assoc., 1932, cii, 1714.
    (*b*) STONE, C. T., HARRIS, T. H., and BODANSKY, M.: The treatment of polycythemia vera, Jr. Am. Med. Assoc., 1933, ci, 495.
    (*c*) GIFFIN, H. Z., and ALLEN, E. V.: Control and complete remission of polycythemia vera following prolonged administration of phenylhydrazine hydrochloride, Am. Jr. Med. Sci., 1933, clxxxv, 1.
11. (*a*) ALLEN, E. V., and BARKER, N. W.: Experiments with phenylhydrazine. III. Pathologic anatomy, ANN. INT. MED., 1928, i, 683.
    (*b*) BASSETT, S. H., KILLIP, T., and MCCANN, W. S.: Mineral exchanges of man. III. Mineral metabolism during treatment of a case of polycythemia vera, Jr. Clin. Invest., 1931, x, 771.

12. HUEPER, W. C.: Pathologic studies on the organic effects of various hydrazine derivatives, Jr. Indust. Hyg. and Toxicology, 1936, xviii, 17.
13. (*a*) MORRIS, R. S.: Erythremia, a therapeutic suggestion, Jr. Am. Med. Assoc., 1933, ci, 200.
(*b*) BRIGGS, J. F., and OERTING, H.: Influence of gastric lavage on familial and non-familial erythremia, Minnesota Med., 1935, xviii, 499.
14. HEATH, C. W.: Oral administration of iron in hypochromic anemia, Arch. Int. Med., 1933, li, 459.
15. HURTADO, A.: Studies at high altitude. Blood observations on the Indian natives of the Peruvian Andes, Am. Jr. Physiol., 1932, c, 487.
16. HEATH, C. W.: The volume and hemoglobin content of the red blood corpuscles in the light of recent knowledge of anemia, New Eng. Jr. Med., 1933, ccix, 173.

CASE REPORTS

PERIARTERITIS NODOSA WITH A CASE REPORT*

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DIFFUSE vascular lesions with bizarre clinical symptoms of general systemic infection have been reported under various names both in this country and abroad. Because the majority of these cases, unfortunately, have not been diagnosed during the course of the illness, it is apparent that one should keep in mind the possibility of periarteritis nodosa in patients with indefinite symptoms of infection without known etiology and in which all the laboratory studies throw no light on the case.

As one of these, we wish to present the following case of periarteritis nodosa which was missed clinically and even on gross postmortem examination. The final diagnosis was arrived at only after careful study of microscopical sections.

CASE REPORT

Mrs. L. W. (aged 64) was first seen April 12, 1936 with a chief complaint of pain in the legs for the preceding two months. The pain was bilateral, below the knees, especially on the left, cramp-like in character, located in the area of the gastrocnemius, present only when the legs were dependent, and always disappearing when the legs were elevated. There was no change in the color or temperature of the skin. Symptoms referable to the various systems were negative, except for "asthmatic influenza" last winter which kept the patient in bed for three weeks. Examination revealed an aged, white, decrepit female. Skin was dry. Pupils were equal and reacted to light and in accommodation. Ears, nose, throat, heart, lungs, and abdomen were negative. The blood pressure was 158 systolic and 80 diastolic. The extremities were normal in color and their color did not change with changes in position. There was a normal palpable pulsation of the popliteal and dorsalis pedis arteries. There were several varicose veins that filled with dependency and emptied with elevation. Reflexes were entirely normal. The clinical impression at this time was that the pain was circulatory in nature, and due probably to inadequate venous return. On April 13, 1936, the red blood cell count was 3,900,000; white blood cell count 14,350; hemoglobin 55 per cent; polymorphonuclear leukocytes 84 per cent and lymphocytes 16 per cent. The red blood cells were large and irregularly-shaped. The urine was acid, showed no albumin or sugar, and the microscopic examination showed a few pus cells with an occasional granular cast. The patient at this time was put on iron medication (ferrous sulphate) and advised to wear bandages on both legs.

For two weeks, with the bandages, there was no leg pain. On May 2, 1936, however, she began to feel remarkably weak and developed pain and numbness from the elbow to the finger tips of the right hand. This lasted two days. The temperature was 98° F. Examination of the arm revealed nothing abnormal; the heart was found normal and the general examination gave negative findings. The patient was

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put on large doses of yeast with the possibility in mind of a vitamin B deficiency. She felt fairly well for four days, and then, in addition to the great weakness, she showed an inability to walk. She was seen again on May 8, 1936, and at this time complained of sharp shooting pain in both legs, despite the bandages which had been worn constantly. The temperature at this time was 102° F. The tongue for the

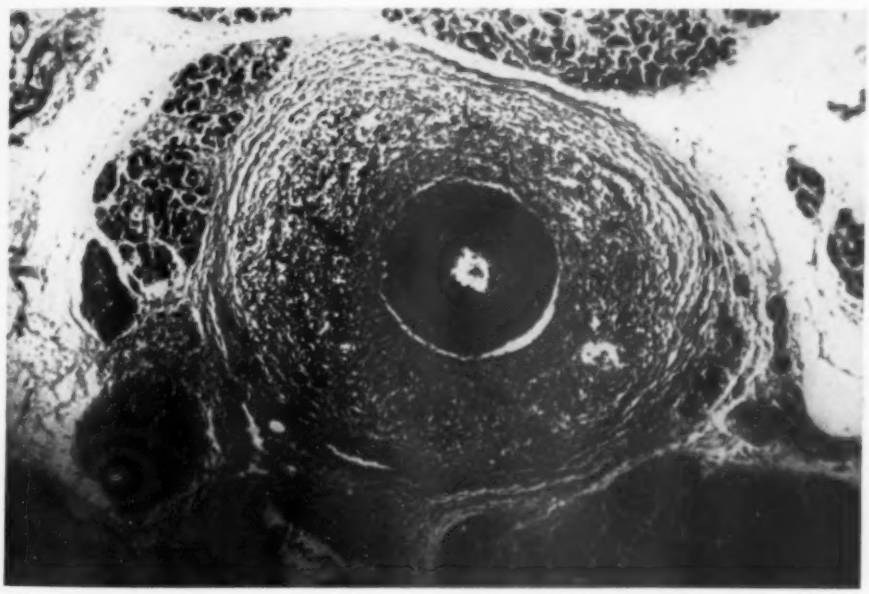

FIG. 1. Medium sized artery of the pancreas showing thrombosis and canalization. Marked hypertrophy and leukocytic infiltration throughout the layers and intimal degeneration. (100 ×.)

first time was smooth, red and painful. Physical examination otherwise was negative. On May 9, 1936, temperature was still 102°; in addition to the glossitis, there was noted for the first time altered sensation including vibratory sense in both legs with bilateral foot drop. The arms were normal both symptomatically and objectively.

The patient was admitted to Montefiore Hospital on May 10, 1936 with a provisional diagnosis of nutritional anemia, possibly pernicious anemia. On May 11, 1936 she developed tingling and sharp shooting pain in the right arm and two days later in the left arm. Both became progressively worse until there was complete loss of use with disappearance of position sense, pain and thermal sensation, and bilateral wrist drop. The temperature was 101° F., pulse 120, and blood pressure 160 systolic and 90 diastolic. Significant findings were mainly neurological. The tongue was smooth and red. There were diminished reflexes in the upper extremities and absent reflexes of the lower extremities, motor weakness in all extremities especially in the right arm, and atrophy of the hands. There was loss of vibratory and position sense of the lower extremities. Neurological diagnosis, in view of the history and laboratory findings, was posterolateral sclerosis, and the patient was put on liver by mouth and parenterally.

Laboratory findings confused rather than clarified the picture. The blood Wassermann and Kahn were negative, and the spinal fluid examination was negative. Gastric analysis showed hypochlorhydria. The urine showed a trace of albumin, occasional hyaline casts, and 4 to 6 pus cells per field. The blood non-protein nitrogen

was 40 mg. per cent. Examination of the urine for heavy metals was negative. On admission the blood examinations showed 63 per cent hemoglobin; 3,430,000 red blood cells; 16,250 white blood cells; and 91 per cent polymorphonuclear leukocytes. Reticulocytes remained less than 1 per cent in spite of therapy; the red cells appeared microcytic and there was no stippling. The blood count did not change materially during the stay in the hospital. Roentgenologic examination of the digestive tract showed no abnormalities.

FIG. 2. Arteriole (section of the liver) showing complete obliteration of the lumen, perivascular infiltration with leukocytes. Fibrosis and hyaline degeneration of the media. (100 ×.)

Throughout the patient's three week stay in the hospital the neurological findings did not change. The blood picture remained the same despite liver, vitamin B, HCl, iron, and transfusion of 300 c.c. of blood on three occasions. The major complaint was weakness, and this became progressively more severe. On May 27, the patient had a brief syncopal attack characterized mainly by severe abdominal pain and dizziness while lying quietly in bed. This did not recur. There were daily rises of temperature to 101°, the pulse running constantly between 100 and 120. The patient left the hospital on June 2, 1936 still not definitely diagnosed, the diagnosis of toxic polyneuritis, cause unknown, being retained for want of something better.

At home the patient became progressively worse. She continued to complain of marked weakness, and the neurological picture remained unchanged. Physical examination otherwise remained negative, except for a few râles in both bases. The blood pressure was 180 systolic and 100 diastolic. On June 3, patient began to vomit all food and liquids, lost her voice, and became distended. This continued until June 6, when she died.

Autopsy performed several hours later showed on gross examination an extremely emaciated white adult female about 65 years of age, with marked pallor of the skin and mucous membranes. Superficial glands were not palpable. Abdomen was flat and no palpable tumors were present. The extremities showed marked

atrophic changes of the extensor muscles and thenar and hypothenar eminences of the palms. The abdominal organs were found in normal positions and relations. Patchy discolorations were present in the walls of the ileum and jejunum. Mesenteric lymph nodes were enlarged. The mesentery was studded with minute yellow gray nodules, firm in consistency. Several of these were visible on the serous covering of the

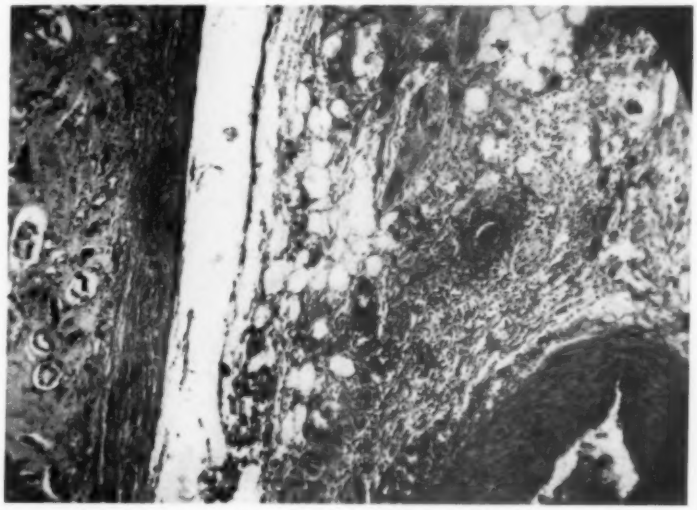

FIG. 3. Showing blood vessels of the kidney. The smaller vessels are involved in an inflammatory reaction while the large sized vessels are free from such reaction. (50 ×.)

bowels. No masses were found. The stomach and large bowel were distended with gas. The liver weighed 1200 grams, had a thick fibrotic capsule, and on cut surface showed mottling of gray areas on a purplish-red background. The spleen was twice normal size, had a thickened capsule, and on cut surface showed marked interstitial fibrosis. The kidneys were atrophic and sclerotic with coarse granulation of the cortex. The adrenals appeared normal. The lungs disclosed old pleuritic adhesions with fibrosis and calcification of both apices. There was edema and congestion of the bases. The heart was pale with flabby myocardium. Excessive subepicardial fat was present. The valves were intact. The coronaries were free from arteriosclerotic changes, though discrete atheromatous patches were seen in the intima of the aorta. The meninges were slightly injected and the cerebral vessels were free from arteriosclerotic changes. There was moderate edema of the brain, but no neoplasm or hemorrhage. The spinal cord showed no gross lesions. The gross anatomical diagnoses were: Marked anemia; chronic myocardial degeneration; congestion and edema of lungs; chronic mesenteric lymphadenitis; ileitis; septic splenitis; edema of brain; bilateral symmetrical atrophy of the upper and lower extremities; and chronic perihepatitis.

Relevant microscopical examination showed marked inflammatory and degenerative changes of medium sized arteries and arterioles in the following organs: liver, kidneys, pancreas, mesentery and spleen. The brain, heart, lungs and adrenals were free from such changes. The nature of the inflammation consisted of several stages of the same process. Some involved the adventitia with marked perivascular infiltration of polymorphonuclear cells. Others involved both the media and adventitia; while in the third group, all three layers were involved with hyaline degeneration, thickening of intima and media with obliteration of the lumen and areas of aneurysmal

dilatation. Sections of the spinal cord did not reveal any cause for neurologic changes in the extremities. Histological diagnoses were: periarteritis nodosa of visceral vessels; chronic myocardial degeneration; edema of brain; and chronic nephritis.

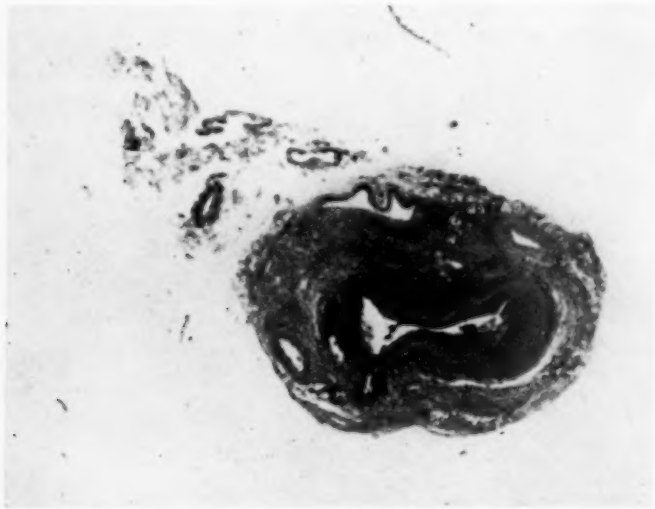

FIG. 4. Arteriole from mesenteric branches showing marked narrowing of the lumen due to hypertrophy and hyalinization of the intima. Fibrosis of the media and some perivascular infiltration. (50 ×.)

DISCUSSION

In a review of the literature, the terminology for this condition is found to differ slightly with various authors: periarteritis nodosa, polyarteritis acuta nodosa, and panarteritis. The first description was published in 1865 by Kussmaul and Maier who named the disease periarteritis nodosa and stated that it consisted of inflammatory changes around the adventitia of small arteries and arterioles resulting in multiple nodules along the course of the vessels. Later, Dickson,[1] in 1908, after summing up the literature, differentiated the lesions under two headings. One group was caused by syphilis and was called periarteritis nodosa; while the second group was caused by some unknown infection or toxin and was called polyarteritis acuta nodosa.

As to etiology, Mott and Barton believe that the disease is a luetic manifestation which involves small arteries frequently including the coronaries and occasionally the cerebral vessels. Derick and Hass' report [2] contains an interesting discussion of the etiology of this disease in which they doubt that periarteritis nodosa is a separate entity at all and believe, in view of their case, that the syphilitic virus is most likely the cause of the arteritis. Their case was one of arteritis of syphilitic origin in a young adult which was diagnosed only after microscopic study of the lesions. They found inflammatory lesions of the small arteries with involvement of all the layers and of periarteriolar tissues, many vessels showing partial or complete occlusion of the lumina with thickening of the intima and thrombosis. Boyd [3] and others, on the other hand, believe that syphilis is not an etiological factor in periarteritis nodosa. The

argument supporting this latter view is that syphilitic lesions are generally found in the elastic type of blood vessels, while periarteritis nodosa is a disease of the muscular type of artery. Though it is true that in several such cases reported in the literature there have been positive serological findings for syphilis, which led the authors to assume that the syphilitic virus was an etiologic factor in their cases, one should not overlook the fact that syphilitic patients may have periarteritis nodosa superimposed as a distinct disease process. Furthermore, even though the literature does not disclose the isolation of a single etiologic factor, aside from the little supported view of infection by unknown filterable viruses, periarteritis nodosa is definitely a clinical and pathological entity.

Clinically, the disease is rare and its diagnostic criteria are not sharply defined. No age is exempt and the occurrence is four to one in males. The clinical manifestations are so varied and bizarre that they may easily simulate a dozen or more diseases. A few of the commonest conditions with which it may be confused are trichiniasis, neuritis, miliary tuberculosis, gastro-enteritis, endocarditis, vascular nephritis and acute abdominal conditions. As to signs and symptoms, those of sepsis predominate, the commonest findings being fever, leukocytosis with or without eosinophilia, moderate to marked anemia, enlargement of the spleen, prostration and loss of weight. Localized manifestations, depending on the locations of the main vascular lesions, are anginal attacks in coronary involvement, symptoms of "acute abdomen" in mesenteric vascular lesions, and polyneuritis in neuro-muscular lesions. It follows, therefore, that diagnosis is extremely difficult during life unless there are peripheral nodules, resection and microscopic examination of which give the diagnosis, or unless, as in the case reported by Bernstein,[4] biopsy of skeletal muscle discloses the disease. Unfortunately, however, the majority of cases do not show peripheral nodules but, as in our case, only lesions which are confined to vessels of the viscera thus making pre-mortem diagnosis impossible. An autopsy study with careful microscopic examination of the blood vessels is then the only method of diagnosing the disease. In this connection Haining and Kimball[5] pointed out that in this country we do not perform autopsies frequently enough, for in their excellent review of approximately 150 cases of periarteritis nodosa they found the majority recorded in foreign literature because of the greater number of routine autopsies carried out in clinics abroad.

Pathological findings and descriptions are fairly uniform in the majority of cases recorded. Gross lesions consist of small nodulations varying in size from that of a lentil to a split pea along the affected vessels. These nodules often involve the mesenteric vessels, but when the visceral vessels are the only ones involved, it is very easy to overlook gross changes by the naked eye. The lesions occur in the following organs and tissues in the order of their decreasing incidence: kidneys, heart, liver, gastrointestinal tract, pancreas, mesenteric arteries, muscles, and peripheral nerves. The central nervous system is least involved. Microscopically, various stages of inflammatory reaction and healing are seen in the walls of the small arteries and arterioles. In the early stage, the exudative process consists of polymorphonuclear infiltration of both the media and adventitia. Later, there are proliferative changes of the intima with subsequent thrombosis and occlusion of the lumen with or without dilatation above this site. In the late stages of the disease polymorphonuclear cells are few and

lymphocytes predominate and hyalin and fibrous tissue replace most of the layers of the vessels.

Summary

In a case of periarteritis nodosa, clinical observations, postmortem findings and a brief discussion of the subject are presented. The case is of further interest because, despite the mesenteric lesions and small infarctions of the bowel, no acute abdominal symptoms were present. Furthermore, the microscopic studies of the spinal cord did not explain the cause of pronounced neuritis of the extremities. Finally we would like to emphasize the value of routine postmortem examinations, especially in those cases of unknown sepsis, for without postmortem study certainly the diagnosis of this condition will be missed.

BIBLIOGRAPHY

1. Beattie, J. M., and Dickson, W. E. C.: A textbook of pathology, 1926, C. V. Mosby Co., St. Louis, p. 556–555.
2. Derick, C. L., and Hass, G. M.: Diffuse arteritis of syphilitic origin, Am. Jr. Path., 1935, xi, 291–307.
3. Boyd, W.: Pathology of internal medicine, 1932, Lea and Febiger, Philadelphia.
4. Bernstein, A.: Case without peripheral nodules, diagnosed antemortem, Am. Jr. Med. Sci., 1935, clxl, 317–325.
5. Haining, R. B., and Kimball, T. S.: Polyarteritis nodosa, Am. Jr. Path., 1934, x, 349–360.

A CASE PRESENTING PULMONARY AND OSSEOUS LESIONS PRESUMABLY DUE TO SARCOID *

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Except among dermatologists, whose chief interest is confined to the skin manifestations, one rarely hears of sarcoid. The fact that there may be extensive involvement of the viscera and bones in addition to skin lesions appears to be quite generally unknown among internists though such cases were described over 20 years ago. When the skin manifestations are slight or even absent and the other lesions pronounced, a difficult diagnostic problem is presented as the case here reported illustrates.

Case Report

W. C., aged 14 years, was referred to me January 16, 1929, for examination because of cough. His general health had been good except that he suffered considerably from sinus disease. It had been observed that the cough was worse when he was having discharge from his sinuses. His appetite was excellent. He was quite free from symptoms other than the cough.

Examination: He was a frail lad with a flat, narrow chest. Height 65 inches; weight 105 lbs. Cervical glands showed slight enlargement. Pulse was 72 and temperature normal. The tonsils did not appear to be infected. With inspiration there was retraction of the lower third of the sternum and also of the epigastrium. There

* Presented at the Detroit meeting of the American College of Physicians, March 5, 1936.

† Deceased.

was a suggestion of increased whisper interscapularly but not enough to be significant. Roentgen-rays of the lungs (figure 1) by Dr. Eliot S. Cogswell showed some thickening at the roots and a certain amount of fine dappling throughout the lung fields. There were also some clusters of pin-head-size rather "soft" shadows.

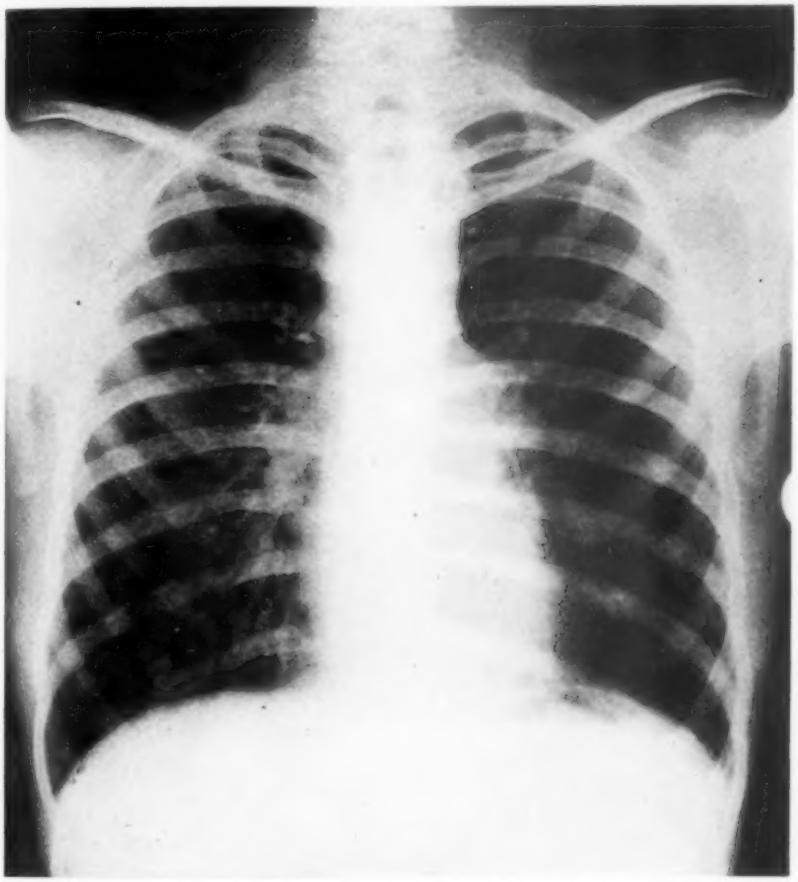


FIG. 1. June 1929. A fine mottling is evident in the right midpulmonic field and one of less extent in the upper outer part of left lung. Physical signs were negative except for an indefinite D'Espine sign.

I was somewhat in doubt as to the significance of the roentgen-ray findings but felt that they were compatible with a chronic, non-tuberculous type of infection and probably were dependent upon his recurring attacks of sinus trouble.

After ascertaining that the patient was not running a fever, I felt that it was probably not a tuberculous process. I next saw him June 10, 1929 (five months later). He was very well, having been free from sinus trouble and gained 6 lbs. in weight. He exhibited interscapular whisper to the fourth thoracic spine. December 27, 1929 (nearly a year after the first examination), he was very well. His weight was 120 lbs., a gain of 15 lbs. since the first examination. There was still slight enlargement of the cervical glands, but no abnormal signs were noted in the chest. There was some mucopurulent discharge present on the postpharyngeal wall. A month later,

while out of the city he had an attack of pneumonia and is said to have been very ill. He made a good recovery and when seen six months later (June 1930) his weight was 126 lbs.—an additional gain of 6 lbs. in six months. He appeared then to be in excellent health except that five weeks previously the middle finger of the left hand had begun to swell and to be somewhat painful. At the time of my examination there was a definitely spindle-shaped swelling but the overlying skin was not involved. It did not appear to be particularly painful except on motion. A surprising amount of bone destruction was revealed by the roentgen-ray. (Figure 4*a*.)

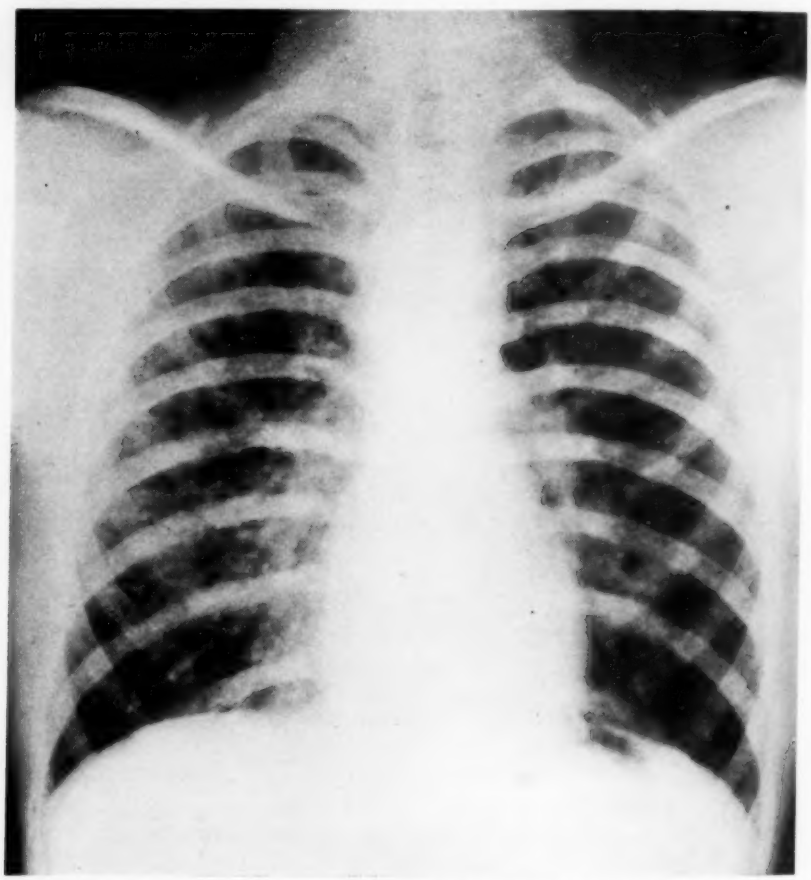


FIG. 2. June 1930. Extensive "snowflake" infiltration of both lung fields somewhat more on the right, with moderate thickening of the hilar structures. Entire absence of physical signs except moderately positive D'Espine sign. General health appeared excellent. Normal temperature.

The roentgen-ray findings of the lungs at this time (figure 2) were even more astonishing. There was extensive, diffuse, soft mottling which was highly suggestive of miliary tuberculosis. From the films alone, one would be quite sure that the lesion was tuberculous; yet he was in excellent health, had gained in weight, was free from fever and with no physical signs of pulmonary disease. The destructive lesions of the bones of the hand were very suggestive of tuberculosis, yet the only pain he experienced was due to a fracture at the site of one of the lesions.

The lung findings were somewhat like the peribronchial, streptococcus pneumonia that occurred during the war, but it seemed unlikely that the lesion as revealed by the roentgen-ray would have persisted for six months. The indolent character of the lesion of the finger was unlike a streptococcus infection. A negative Wassermann appeared to exclude syphilis. I did not know what the pulmonary condition was, nor could I explain the destructive lesion in the bones. Tuberculosis was a strong possibility yet this diagnosis did not ring true.

A protection for the fractured finger was supplied and he was sent to a boys' camp where he was directed to engage in the usual camp activities except that he was to

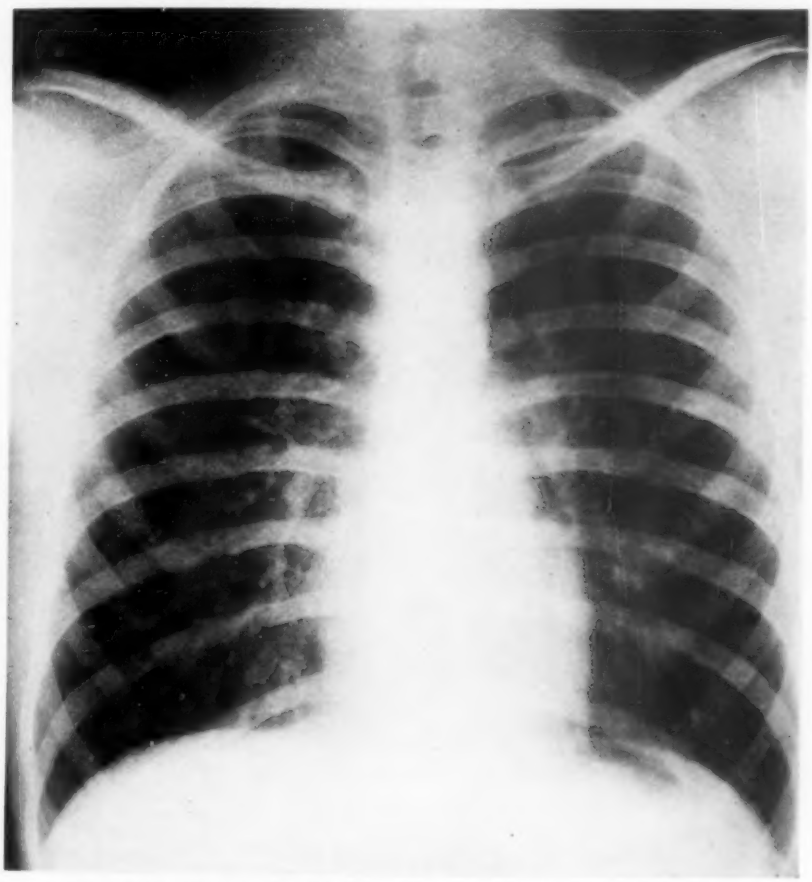


FIG. 3. June 1931. Lungs completely cleared. Hilar structures less dense. This film is even clearer than the one taken in June 1929 (figure 1) which suggests that the process, that was full-blown in June 1930 (figure 2), had really begun when the first film was taken. The attack of streptococcus pneumonia developed about mid-way between films one and two.

avoid all strenuous exercise such as athletic contests, etc. A rest period each afternoon was also prescribed. During the summer he gained 9½ lbs. and was free from fever and cough. Roentgen-rays of the lungs at this time showed practically no change but the bony lesion (figure 4*b*) showed much improvement. There was no pain unless he grasped something very hard with the hand.

In June 1931, after spending the winter in Texas, he was in excellent shape. His

A B C

FIG. 4. (*a*) Proximal end of the first phalange of left middle finger shows a destructive lesion with fracture. The proximal end of the middle phalange of the ring finger shows a similar but less marked lesion. (*b*) Two months later definite improvement evident. (*c*) One year after *a*. Bone lesions have entirely subsided.

weight at this time was 136 lbs. 6 oz., a gain of over 31 lbs. since the first examination 2½ years before. He was free from cough and the roentgen-ray of the lungs (figure 3) showed them to be entirely clear; better in fact, than at the time of my first examination. It seems probable that the findings noted in the first film, and absent in the last one, were due to the beginning of sarcoid which, by the time the next film (figure 2) was taken, had progressed. When last seen the bone lesions had entirely subsided (figure 4*c*).

By this time I felt sure that the condition was not tuberculosis though it was not until four years later, when Dr. Francis T. Hunter showed me the film of a similar case at Massachusetts General Hospital, that I realized that the condition was probably sarcoid. Dr. Hunter has since published his case, and the controversial points as to the priority of its recognition and the different views as to the etiology are dealt with in his presentation.

Discussion

Sir Jonathan Hutchinson appears to have been the first to describe one of the skin manifestations of this interesting disease nearly a quarter of a century before Boeck's article appeared. The latter gave a detailed report of the histology and suggested the name "Sarcoid" (sarcoma-like) because of the infiltrative tendency somewhat suggesting the lymphoblastoma group.

Considered first a disease of the skin, it was not until 1902 that Kienbock [2] reported what he designated as "bone cysts" in a case of sarcoid. In 1915, Kugnitsky and Bittorf [3] described visceral lesions showing the same histologic picture in the lungs, bronchial glands and other viscera. By some the condition is considered a manifestation of tuberculosis. Those championing this etiology explain the almost universally negative tuberculin reaction and the failure to find tubercle bacilli in the lesions, to what they term a condition of "anergy"—a relative or complete stage of desensitization. Goeckerman [4] and Sulzberger [5] among others, present arguments in support of a tuberculous etiology. The subject of sarcoid was discussed at length by the European dermatologists in 1934. Jens Nielsen,[6] chief of clinic of the Finsen Institute, Copenhagen, considers it a definite clinical entity. He observed that there was pulmonary involvement (including bronchial glands) in 37 of 46 cases with skin manifestations. In none of them were there clinical or stethoscopic signs of pulmonary involvement.

The condition is benign, torpid and very chronic. Nielsen mentions the possibility of complete resolution but states that the pulmonary lesions are more apt to be stationary. For this reason the case here reported is unique in the rapidity with which the lung cleared. Piérard [7] says that the pulmonary lesions are characterized by proliferation; they are not exudative in type and there is no tendency to break down and form cavities. Nor do they show a tendency to heal with the production of calcium. There is a lack of peribronchial pattern of lesions, and absence of calcification and of cavity formation. The roentgenogram may resemble miliary tuberculosis, or miliary carcinomatosis, or periarteritis nodosa. In all of these, however, the patient is acutely ill. It is also said to resemble the "sand-paper" mottling of leprosy. Typical sarcoid tissue has been found in the lungs at autopsy. The "bone cysts" (*osteitis multiplex cystica*) are fairly frequent and most common in the bones of the hands and feet. In the case here reported they healed with surprising rapidity as the roentgen-rays show. Kissmeyer,[9] likewise, considers the disease a specific, chronic granulomatous process, standing midway between tuberculosis and leprosy.

No skin lesion was noted in the patient here described. This should not be interpreted as excluding a small inconspicuous lesion that might easily have been overlooked or thought to be of no consequence. However, members of his family do not recall any skin lesions. Increasing knowledge of the disease may demonstrate that skin lesions are not always present.

Various drugs have been tried with results that are not convincing. In this case, under a régime of outdoor life, with moderate exercise, a great deal of rest and a well-balanced and abundant diet, the recovery was prompt and complete, both the osseous and pulmonary lesions completely resolving.

Summary

A case believed to be sarcoid of the lungs and bones is presented in which skin lesions were absent or minimal. Complete recovery, as demonstrated by roentgenological study, took place with surprising promptness under a régime of somewhat restricted exercise, ample rest and a generous, well-balanced diet.

REFERENCES

1. Hunter, F. T.: Hutchinson-Boeck's disease (generalized "sarcoidosis"); historical note and report of case with apparent cure, New Eng. Jr. Med., 1936, ccxiv, 346–352.
2. Kienbock, R.: Quoted by Hunter in his bibliography.[1]
3. Kugnitsky and Bittorf: Quoted by Hunter in his bibliography.[1]
4. Goeckerman, W. H.: Sarcoids and related lesions; report of 17 cases; review of recent literature, Arch. Dermat. and Syph., 1928, xviii, 237–262.
5. Sulzberger, M. B.: Sarcoid of Boeck (benign miliary lupoid) and tuberculin anergy; report of case and general remarks, Am. Rev. Tuberc., 1933, xxviii, 734–745.
6. Nielsen, J.: Recherches radiologiques sur les lésions des os et des poumons dans les sarcoïdes de Boeck, Bull. Soc. franç. de dermat. et syph. (Réunion dermat., Strasbourg), 1934, xli, 1187–1218.
7. Piérard, J.: Le granulome annulaire doit-il être rangé parmi les sarcoïdes de Boeck? Bull. Soc. franç. de dermat. et syph. (Réunion dermat., Strasbourg), 1934, xli, 1275–1278.
8. Kissmeyer, A.: La maladie de Boeck; Sarcoïdes cutanées bénignes multiples, 1932, Levin and Munksgaard, Copenhagen, Denmark.

EDITORIAL

SNAKE VENOM IN HEMORRHAGIC STATES

THE value of moccasin venom in the control of hemorrhage was pointed out by Peck and Rosenthal.[1] Peck had earlier found that moccasin venom would produce a refractory state to experimental purpura, or the Shwartzman phenomenon. For a number of years venom of various snakes has been suggested for innumerable diseases, but more definitely in relation to the production of hemostasis by direct application to the bleeding area. It was not until the work of Peck and Rosenthal with the parenteral use of moccasin venom that definite improvement was obtained in certain so-called secondary hemorrhagic states. The exact action of the venom is not known, but it has been assumed that the action is due to a change in the capillary walls resulting in a lessening of their permeability and thus preventing extravasation of blood. Moccasin venom was chosen because it seemed to produce the best results, although some improvement has been obtained with the venom of the copperhead. Cobra venom, since it is largely neurotoxic, has been used with fairly satisfactory results in cases of intractable pain.

Peck and Rosenthal in 1935 reported a series of cases of secondary and primary blood dyscrasias, with particularly good results in that group of diseases associated with some abnormality of the vascular wall. The dose recommended and used most generally is, for patients ten years old or older, an initial subcutaneous injection of 0.4 c.c., with a rapid increase in the dose on subsequent injections to 1.0 c.c. as a maximal. The reaction of sensitivity, which occurs in most patients on the third or fourth injection, is characterized by a local area of heat, redness, and swelling without much evidence of systemic reaction. At this time desensitization should be carried out by reducing the dose to a minimal quantity, approximately 0.05 c.c. This is maintained until all evidence of reaction disappears, at which time the dose may be gradually increased to the full amount of 1.0 c.c. twice a week. After hemorrhage has been controlled, the interval between injections may be lengthened to a week or longer depending upon the severity of the original hemorrhagic condition.

Moccasin venom has proved to be of definite value in the treatment of idiopathic epistaxis, bronchiectasis with hemoptysis, and functional menorrhagia, and fairly satisfactory in the treatment of toxic or secondary pur-

[1] PECK, S. M., and ROSENTHAL, N.: Effect of moccasin snake venom (Ancistrodon Piscivorus) in hemorrhagic conditions, Jr. Am. Med. Assoc., 1935, civ, 1066–1070.

PECK, S. M., CRIMMINS, M. L., and ERF, L. A.: Coagulating power of Bothrops Atrox venom on hemophiliac blood, Proc. Soc. Exper. Biol. and Med., 1935, xxxii, 1525–1527.

PECK, S. M., ROSENTHAL, N., and ERF, L. A.: The value of the prognostic venom reaction in thrombocytopenic purpura, Jr. Am. Med. Assoc., 1936, cvi, 1783–1791.

puric states. Peck and Rosenthal also had fairly good results in cases of hereditary multiple telangiectasis; they reported four cases, in two of which very definite improvement was obtained. They emphasized the fact that in this particular condition it is important to continue the use of venom over a long period of time. In diseases associated with changes in the blood, such as thrombocytopenic purpura, fairly good results were obtained and a definite response was noted in the majority of cases in their group. In certain instances improvement was obtained without affecting any change in the blood itself, which would seem to bear out the contention that the action of venom is primarily upon the blood vessels. On the other hand, cases of hemophilia, aplastic anemia, and leukemia show little response to venom therapy.

In 1936 Watkins and Mussey [2] confirmed the findings of Peck and Rosenthal in cases of functional menorrhagia, and in 1937 Watkins and Thompson reported a series of twelve cases of essential hematuria, in eleven of which there was cessation of hemorrhage.

It would seem, at least at present, from the work that has been done that moccasin venom is of definite value in the control of certain types of hemorrhagic conditions. However, the experience with the venom has as yet been too limited to state what the ultimate results will be. In some instances recurrences have been noted which may be controlled by resumption of the use of venom; in other instances there seems to be complete cessation of all hemorrhage. Until the material has been in use over a longer period of time, and its use confined to secondary hemorrhagic states, it will be difficult to determine its real efficacy in the permanent control of hemorrhage.

C. H. W.

[2] Mussey, R. D.: Discussion, Proc. Staff Meet. Mayo Clinic, 1936, xi, 263–264.
Watkins, C. H.: Experience with snake venom in menorrhagia, Proc. Staff Meet. Mayo Clinic, 1936, xi, 261–263.
Watkins, C. H., and Thompson, G. J.: Results in treatment of essential hematuria with moccasin venom, Proc. Staff Meet. Mayo Clinic. (In press.)

REVIEWS

Applied Dietetics for Adults and Children in Health and Disease. By SANFORD BLUM, M.D. 408 pages; 24 × 16.5 cm. F. A. Davis Company, Philadelphia. 1936. Price, $4.75.

This book has many shortcomings. Published as a new book, it is essentially a revised and enlarged edition of "Practical Dietetics for Adults and Children in Health and Disease" published as a second revised edition in 1926. The present volume follows practically the same formula as its forbear of 10 years ago. It is divided into two parts, the first of which is entitled "Dietary for Adults in Health and Disease"; the second, "Dietary for Infants and Children in Health and Disease." Diets are arranged alphabetically according to the title of the healthy or disease state. In comparing the 1926 and 1936 editions there is little to show that advances have been made in the field of dietetics.

To be sure there are new sections as, for example, those on pernicious anemia, carcinoma of stomach, diverticulitis, gall-bladder infection, gonorrhea, hemorrhage from stomach, indigestible foods and combinations, inorganic elements essential to nutrition, pneumonia, salt-free diet, and salt-poor diet. There is also some elaboration of the sections devoted to colitis and diabetes including a discussion of diet with insulin therapy. Occasionally a good deal of common sense is condensed into short chapters such as those devoted to "Dietetics Fads and Fallacies" and to "Vitamins." Incidentally there are practically no changes in Part II of the volume in the 10 year period from 1926 to 1936.

It is difficult to discuss the specific diets offered in this book without being too critical. Perhaps it will suffice to say that many of the diets are far too inadequate and cannot possibly accomplish the end result for which they are prescribed. Very often the choice of foods is without scientific basis. Furthermore it is doubtful whether a person's occupation, be it business or society, woman or college professor, really plays a *predominant* rôle in the selection of a specific diet. Such notations are dramatic rather than instructive.

In brief, then, this book has not kept abreast of advances in medicine. It represents one of that group of compendiums which in trying to be of service to the busy practitioner often mislead him in his selection of diets as well as in his knowledge of the essentials upon which careful dieting is based.

S. M.

Dietetics for the Clinician. By MILTON ARLANDEN BRIDGES, M.D., B.S., F.A.C.P. Third Edition. 1055 pages; 24 × 15 cm. Lea and Febiger, Philadelphia. 1937. Price, $10.00.

Although the general plan of this third edition has not been changed the book has grown in size from 666 to 970 to 1055 pages through its three editions. According to the author the present volume represents "a relatively new text-book based upon more accurate and up-to-date foundations."

Examination discloses a remarkable and comprehensive treatise. All of the good features of the two previous editions have been retained and in addition the subject matter has been augmented and rewritten so that it becomes one of the most useful reference books in the field of dietetics. The sections prepared by specialists are a feature of the book. Some overlapping and repetition result but these have been reduced to a minimum.

The material pertaining to the mechanics, physiology and chemistry of digestion has been markedly condensed and shorn of extraneous, non-practical discussion. For

convenience, the various disease entities are arranged alphabetically and presented according to the following general plan. Each disease is first the subject of a brief general discussion after which there follows a detailed listing of those foods to be omitted, as well as those allowed in limited quantities. Finally, there is a presentation to the reader, and hence to the patient, of a series of practical edible items of food, readily obtainable, arranged in accordance with the previously outlined principles. Wherever indicated there are added a number of practical medical and culinary suggestion.

The author recognizes that dietotherapy is often empirical and that there are diverse opinions regarding the dietary management of many diseases. Previous editions have been criticized for inconsistencies between the diet and the pathological physiology underlying the diseases under discussion. Such criticisms may, however, be omitted, especially since it is apparent that a sincere attempt has been made to include only those diseases in which, in the opinion of the author and his contributors, diet plays a rôle. With some exceptions they have admirably avoided contentious matter.

The food tables are very comprehensive and well arranged. Under "Distribution of Foods" are included lists showing those foods highest or lowest in Ca, I, Fe, Vitamins A, B, etc.; there are also lists showing flatulence-producing foods, fluid foods, soft foods, neutral ash, acid and alkaline-ash foods, etc. It is a comfort to know that data of this kind can be found in one book. Traditional and dietetic evaluation of foods are compared. In the appendix, written in collaboration with Marjorie R. Mattice, are listed numerous other tables replete with information concerning food analyses and showing their nutritive, mineral and vitamin values.

The book will be well received because it supplies with authoritative clarity, and in a practical and detailed manner, valuable information in the field of dietetic treatment.

S. M.

Theory and Practice of Psychiatry. By WILLIAM S. SADLER, M.D. 1231 pages; 26 × 18.5 cm. C. V. Mosby Company, St. Louis, Missouri. 1936. Price, $10.00.

This book was written as a "psychiatric textbook for neuropsychiatric specialists and general practitioners of medicine" and "a reference handbook for psychologists, sociologists, pastors and other professional readers." It consists of 1155 large pages; 2 pages of excellent bibliography, containing almost entirely books rather than articles; 34 pages of glossary and a complete index. It is divided into a good historical introduction which, among other things, outlines the various schools of thought; and five sections.

The first, headed Theory of Psychiatry, 233 pages long, is a résumé of psychology and psychopathology. It contains a great many definitions, a good deal of illustrative material. Part II, Personality Problems, devotes 191 pages to a discussion of personality, classifications of personality, the question of integration, and personality problems at various age levels. Part III, The Neuroses, contains an exhaustive presentation of the author's concept of the origin, characteristics, motivations, symptomatology and treatment of these borderline states. Part IV, in 121 pages covers the Psychoses, that is the major mental illnesses. The rest of the book, Part V, deals entirely with Psychotherapeutics.

The book concerns itself primarily with the study and treatment of non-institutional patients of the sort that may be expected to present themselves to general practitioners. It is exceedingly readable. This is a distinct tribute to a volume of this size. One's interest does not lag at any point, however much one may disagree with the author. Early in his writing he tells us that he personally agrees in most respects

with orthodox views, but he here sets forth utilitarian concepts he finds clinically useful. He is certainly resourceful, never loses sight of the broader aspects of the problem with which he has to deal, and does not hesitate to make use of any means to help restore his patient to health.

We conceive it to be the duty of a reviewer in a special field to give individuals outside his particular branch of medicine his reactions to a book which entirely concerns itself with that special field. We have read most of this large volume twice and have been unable to escape the feeling that this might have been an enduring classic if it had been condensed into 250 or 300 pages. There is much throughout the book which is exceedingly worthwhile. It is a volume which should be read in its entirety or not at all. Otherwise, it is likely to give rise to distinct misunderstandings. An example is the statement on page 477, in which we are told to "laugh heartily at his fears and get him (the patient) to join in the laughter. Ridicule is the master cure for fear." Dr. Sadler is too good a psychiatrist and to kindly a man to imply that we should ridicule the patient himself. In many places he explicitly warns us against doing so. This is typical of many instances throughout the book.

There are many repetitions, there are too complex classifications of personalities —almost as many as there are individual case histories presented. There is very little effort to group them. One gets the impression of hair-splitting minor variations. The chapter on Classifications of Personality, for example, contains a Psychosociologic Classification into 12 groups under such headings as Deficient Personality, Perverted Personalities, Criminal Personalities, etc.; an Intellectual Classification of Personalities; a Sociologic Classification of Personalities; Temperamental Types of Personality; Endocrine Classification of Temperaments, including such statements as: 6. "The Gonad-Dominant Type—This type is generally found to be secretive, sly and deceptive. They are not always outwardly sensual appearing, but thorough acquaintance reveals that their entire lives are motivated by the sex urge"; a Sensory-Motor Classification; a paragraph on Behaviorism and a short section entitled, Other Classifications. We feel that any such discussion as this would be very likely to hopelessly befuddle most individuals and might prove exceedingly misleading to some of the groups, such as pastors and sociologists, for whom the book is written. There are too many vague descriptions of personality distortions or of neurotic pictures. Throughout the book he speaks of such things as Master motives, Master psychobiologic drives, the psychology of self-deception, discussions of self-realization, moral maladjustment, cosmic maladjustment and realizing personality potentials, which seem to us to have little place in a psychiatric textbook, tinged as they are by more than a trace of semi-religious exhortation similar to the type found in so many of the "Know Thyself," "Quest for Happiness" popular psychologies which have flooded the bookstalls in the past few years.

The section on Psychotherapeutics contains a great many exceedingly helpful suggestions and technics. Chapters 68, 69, 72 and 73 are good. There is a timely and worthwhile chapter on the teaching of psychiatry and psychiatrists. Chapter 74, listing and explaining various philosophies of life, is interesting, but the whole 230 pages of this section are so interlarded with what amounts to "pep talks," slogans such as "Hold the fort," "Sand the track," "Play the game square and take the score like a man" as to create a great deal of difficulty in separating the wheat from the sort of chaff best illustrated by his instruction as to the technic of mastering fear, which (page 974) consists in getting the patient to assume the following attitude: 1. Do not fear it; 2. Do not fight it; 3. Do not disown it; 4. Do not try to run away from it; 5. Utilize fear as a fight stimulus; 6. Refuse to foster fear curiosity; 7. Unmask fear; 8. Avoid the fear habit. The tendency to moralize and to make appeals to one's better self are constantly present as in "Conscious conflict, when viewed squarely and faced bravely, is the battle cry of one's better self, calling for the mobilization of all

the powers of the idealism of the personality for the purpose of effecting the psychic conquest and subsequent ethical and moral elevation of one's natural emotional impulses and innate biologic urges." We respectfully submit the point of view that few of us are innately equipped to exhort our patients with sufficient conviction to even send them away from our offices with a temporary glow of well-being, let alone effect lasting benefit.

H. M. M.

Tissue Immunity. By R. L. KAHN, M.S., D.Sc. 707 pages; 23.5 × 17 cm. Charles C. Thomas, Baltimore, Maryland. 1936. Price, $7.50.

This book presents a thorough exposition of the author's ideas on the rôle the tissues in general play in resistance to infection. There is no attempt to substitute one theory of immunity for another, but merely to extend and enlarge the concept of the immunological responses to bacteria and other antigens. These responses are considered a physiological function of all cells and are believed to have their evolutionary origin in parasitism. Tissue immunity is not only philosophically discussed but many experiments are described in substantiation of the author's views. These demonstrate the reaction to an antigen of various tissues in the non-immune state, in the naturally immune animal, at different stages in the rise and fall of acquired immunity, and finally in the condition of "disimmunity." The clinical significance of these responses is given full consideration. Though it is not impossible that exception will be taken to some of the conclusions drawn from the experiments, this book is undoubtedly an important and stimulating contribution to the literature on immunology and one that may be unhesitatingly recommended both to the clinician and to the specialist in this field. It is, however, regrettable that the style of presentation is not more pleasing.

F. W. H.

Heart Disease and Tuberculosis. By S. ADOLPHUS KNOPF, M.D. 108 pages; 20.5 × 14 cm. The Livingston Press, Livingston, New York. 1936. Price, $1.25.

The author has played an active part for many years in anti-tuberculosis work. In this small book he gathers together in brief form many rather disconnected observations upon the present status of preventive methods in both diseases. The importance of diaphragmatic breathing as a preventive and even a curative method is heavily stressed.

M. C. P.

Modern Urology. By HUGH CABOT, M.D. 1813 pages; 24.5 × 17 cm. Lea and Febiger, Philadelphia. 1936. Price, $20.00.

Cabot's Modern Urology is well named for it brings up to date every phase of urology and does it very efficiently. The chapters are written by different authors who are authoritative and who well represent urology in America. The book is in two volumes, is well edited, and is profusely illustrated. The first volume is divided into six sections dealing with the lower urinary tract. It contains a chapter dealing with methods of diagnosis which is unusually informative and a chapter on transurethral resection of the prostate gland, which, while enthusiastically written, is nevertheless a well balanced description of the procedure and its results in the hands of the urologists in this country most proficient in its use. The open types of operation on the prostate gland are also very well described by able and experienced surgeons.

The second volume is divided into four sections, dealing with conditions in the bladder, ureters and kidneys. The chapters on stone present the newer conceptions of stone formation. The article on anomalies of the kidneys and ureters is probably the best and most complete information on this subject that has appeared in years. Tumors of the kidney have been particularly well presented, and the classification of these tumors which is offered is based on sound reasoning. The last section deals with radiation therapy of tumors of the genito-urinary tract. This section discusses the radiosensitivity of cancers and classifies tumors accordingly, and indicates the manner in which these various tumors are to be radiated and the results in a large experience. It is a very valuable section.

Cabot's Modern Urology is a book that every urologist should possess. It should also be accessible to general surgeons, general practitioners and students as the best encyclopedia of urology.

COLLEGE NEWS NOTES

The New Headquarters of the American College of Physicians

In accordance with action initiated by the Board of Regents and the Board of Governors of the College at the 1936 Annual Session, the College acquired by purchase the former residence of Charles J. Eisenlohr at 4200 Pine Street, Philadelphia. The permanent headquarters building is illustrated herewith. The building occupies a plot of ground approximately two hundred feet square, bounded by South Forty-Second Street on the east and by Pine Street on the north. The grounds are beautifully landscaped, with many attractive shrubs, evergreen and deciduous trees. The

Fig. 1. Main entrance.

FIG. 2. View of the garden and building from the south.

FIG. 3. Reception hall and staircase.

FIG. 4. Secretary's office.

FIG. 5. Executive Secretary's office.

house was built in 1906–07 from the architectural plans of Horace Trumbauer, who has attained an enviable position as an architect from the many beautiful and practical buildings he has designed, among them being the new Duke University at Durham, N. C. The following architectural details of the College's new home may be of interest to the members.

"In style it is based on the tradition of the late Eighteenth Century French Architecture of the period of Louis XVI. In composition it consists of a main mass and a lower wing. The main part is sub-divided into a central portion with a pavilion on each end, accented on the first floor with tall windows surmounted by pediments supported on consoles. The main walls are two stories in height and are

FIG. 6. Lounge and Board room.

crowned with rich cornice and high mansard roof, this latter being metal crested and terminating in moulded finials.

"The main body of the walls is constructed of gray buff brick accented by the terra cotta cornice, window, and entrance and porch details.

"The property is surrounded by a wrought iron fence designed in the same general style as the house and is recalled in the house by the wrought iron doors and window grilles at the main entrance and doors to the south porch.

"The decorative treatment of the interior is consistent with the style of the exterior and again follows the Louis XVI style. The rooms are paneled in wood with decorative plaster cornices and marble mantels."

The location is but a few squares removed from the University of Pennsylvania and the Philadelphia College of Pharmacy and Science. Excellent transportation facilities are available through surface and subway-surface trolley lines; furthermore, it is within convenient distance of the new West Philadelphia Station (Thirtieth

Street) of the Pennsylvania Railroad and the Twenty-Fourth Street Station of the Baltimore and Ohio Railroad.

The house answers the long pressing need for adequate offices, committee rooms and a Board room for the College. With a minimum of alteration, the house has been admirably arranged for the work of the College. Spaces are available for the College Library of publications by members, for various meeting rooms and for social gatherings of members. On the second floor are available rooms in which examinations of the American Board of Internal Medicine may be held when these examinations are scheduled for the Philadelphia territory; also rooms where members may conduct private conferences when in Philadelphia.

The members of the College are cordially invited to visit and inspect the new College building and to use it for their headquarters when passing through Philadelphia.

The College Library of Publications by Members

Considerable progress has been made in establishing a College Library of books of which our members are the authors. This Library, in a sense, is a memorial library to our members. A general medical library, other than one composed of publications by the members, is scarcely justified, because there are so many other general medical libraries available in Philadelphia.

A little booklet indexing all the books that have been donated to the College Library will be ready for distribution at the College Booth at the St. Louis Session, April 19 to 23.

We gratefully acknowledge the following recent contributions:

Books

Dr. Ray M. Balyeat (Fellow), Oklahoma City, Okla., one autographed book, "Allergic Diseases: Their Diagnosis and Treatment";

Dr. Charles A. Doan (Fellow), Columbus, Ohio, one autographed book, "Clinical Implications of Modern Physiologic Hematology";

Dr. Harry A. Pattison (Fellow), Livingston, N. Y., one autographed book, "Edward Livingston Trudeau, A Symposium" (with Lawrason Brown, Allen K. Krause and Charles G. Trembley);

Dr. Willard J. Stone (Fellow), Pasadena, Calif., one book, "Bright's Disease and Arterial Hypertension."

Reprints

Dr. M. Coleman Harris (Fellow), New York, N. Y.—1 reprint;
Dr. Samuel E. Munson (Fellow), Springfield, Ill.—1 reprint;
Dr. Robert Sterling Palmer (Fellow), Boston, Mass.—3 reprints;
Dr. John W. Shuman (Fellow), Los Angeles, Calif.—1 reprint;
Dr. Edward L. Turner (Fellow), Nashville, Tenn.—12 reprints;
Dr. Hyman I. Spector (Associate), St. Louis, Mo.—4 reprints;
Dr. Hugh Stalker (Associate), Grosse Pointe, Mich.—1 reprint.

Dr. Elliott P. Joslin (Fellow), Clinical Professor of Medicine, Harvard University Medical School, Boston, delivered the ninth annual Ranson Lecture at Northwestern University, February 3, on protamine insulin.

Dr. Samuel M. Bittinger (Fellow), assistant superintendent of the North Carolina Sanatorium, Sanatorium, N. C., will be the director of the Western North Carolina Sanatorium now under construction, near Asheville. Dr. Paul P. McCain (Fellow), superintendent and medical director of the North Carolina Sanatorium for the Treatment of Tuberculosis, will have general supervision over the new institution.

Dr. Roscoe L. Sensenich (Fellow), South Bend, Ind., has been elected president of the Northwest Medical Conference.

Dr. Thomas Parran (Fellow), Surgeon General of the U. S. Public Health Service, delivered the Gehrmann Lectures at the University of Illinois College of Medicine during March on the subjects: "Health as a Factor in Social Security," "Industrial Hygiene" and "Syphilis."

Dr. Alfred R. Masten (Associate), Denver, has been appointed director of a newly created division of tuberculosis control under the Colorado State Board of Health.

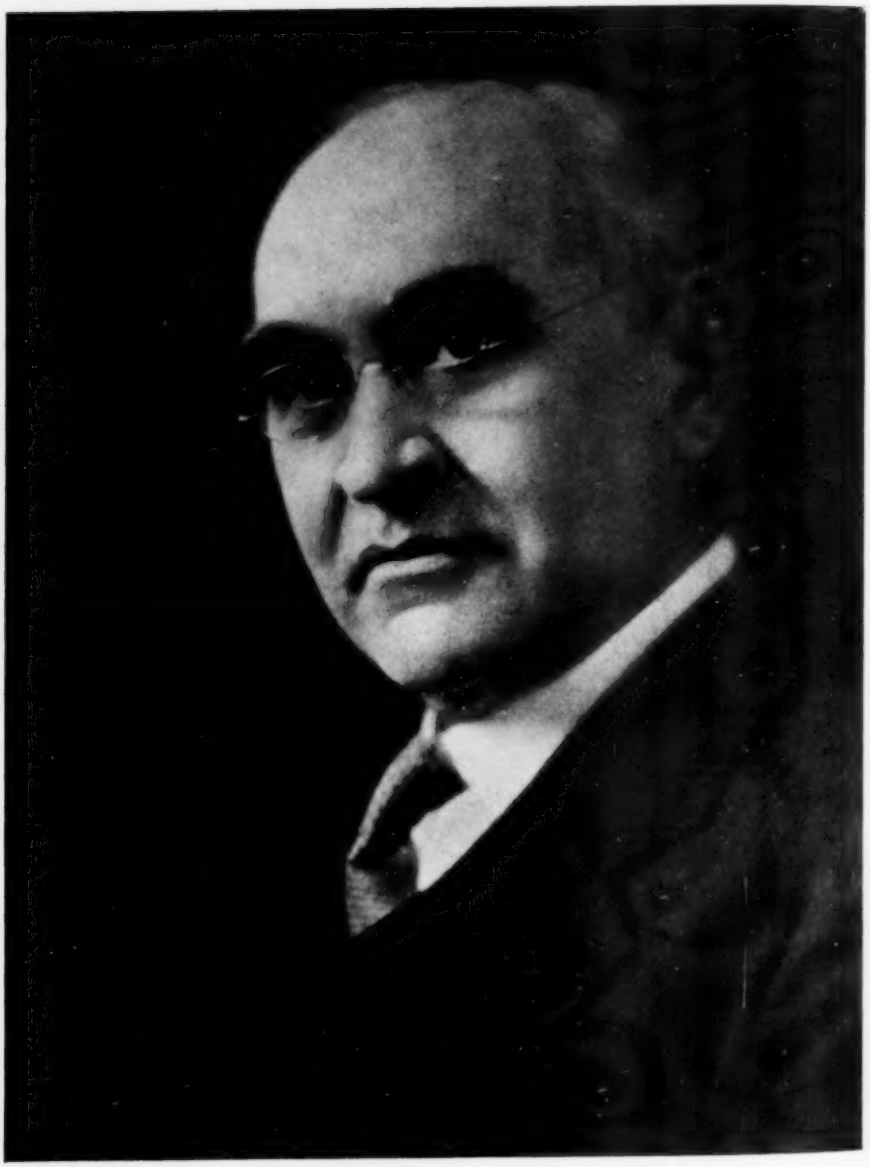
Under the auspices of the Fulton County (Ga.) Medical Society, Dr. Henry W. F. Woltman (Fellow), Professor of Neurology, University of Minnesota Graduate School of Medicine, delivered the E. Bates Block Memorial Lecture in Atlanta, January 28, on the subject, "Postoperative Neurologic Complications."

The fifth annual graduate clinic of the George Washington University School of Medicine, Washington, D. C., was conducted during February, with the following Fellows contributing:

Dr. William E. Clark, "Duodenal Ulcer";
Dr. Walter A. Bloedorn, "Relation of Clinician and Pathologist";
Dr. Roger M. Choisser, "Sudden Death: A Clinical Pathologic Consideration with Case Presentations."

Dr. Henry J. John (Fellow), Cleveland, Ohio, was the recipient of the Eisenman Award of the Cleveland Jewish Welfare Federation at a meeting on February 4, the award being made in recognition of his work for diabetic children in Cleveland.

Dr. Edward B. Krumbhaar (Fellow), Philadelphia, Pa., has been elected vice president of the College of Physicians of Philadelphia.



DR. WILLIAM ALLANSON WHITE

OBITUARIES

WILLIAM ALLANSON WHITE

William Allanson White (Fellow), an eminent physician, a pioneer psychiatrist of international renown and a gallant gentleman, died on March 7, 1937, in his apartment at St. Elizabeths' Hospital of which he had been Superintendent for the past thirty-four years.

Dr. White was born in Brooklyn, New York, on January 24, 1870; graduated from Cornell University in 1889; and from Long Island Medical College in 1891. In the following year he was appointed second Assistant Superintendent of the New York State Hospital for the Insane at Binghamton.

In 1903 President Theodore Roosevelt appointed Dr. White Superintendent at St. Elizabeths, then known as the Government Hospital for the Insane at Washington, D. C., a position which he held at the time of his death. He was Professor of Psychiatry at George Washington University, the U. S. Army Medical School, the U. S. Navy Medical School, and until 1932 at Georgetown University School of Medicine, a position which he relinquished because of pressure of work. He was a Fellow of the American College of Physicians; a member of the National Research Council; a member of the Board of Directors of the National Committee for Mental Hygiene; Ex-President International Committee for Mental Hygiene; Councilor, Medical Council, U. S. Veterans Administration; member and former Secretary Federal Board of Hospitalization; Ex-President American Psychiatric Association; American Psychopathological Society; American Psychoanalytic Society; Psychoanalytic Society of the District of Columbia; The Society of Nervous and Mental Diseases, Washington, D. C.; Medical Society of the District of Columbia, American Medical Association, American Institute of Criminal Law and Criminology; American Neurological Association; American Anthropological Association; Tri-State Medical Association; Washington, D. C. Psychopathological Association; New York Psychiatric Association and many other learned Societies and Associations.

Dr. White was a prolific writer, his articles appearing in the leading medical and scientific journals of this and many foreign countries. He was the author of the following books:

"Insanity and the Criminal Law" (Macmillan).
"The Meaning of Disease" (Williams and Wilkins).
"Mechanisms of Character Formation" (Macmillan).
"Principles of Mental Hygiene" (Macmillan).
"Mental Hygiene of Childhood" (Little, Brown & Co.).
Textbook on Nervous and Mental Disease—with Jelliffe (Lea and Febiger).

"Outlines of Psychiatry"—14th Edition (Nervous and Mental Disease Publishing Company).
"Mental Mechanisms" (Nervous and Mental Disease Publishing Company).
"Introduction to the Study of the Mind" (Nervous and Mental Disease Publishing Company).
"Essays in Psychopathology" (Nervous and Mental Disease Publishing Company).
"Lectures in Psychiatry" (Nervous and Mental Disease Publishing Company).
"Thoughts of a Psychiatrist on the War and After" (Paul B. Hoeber).
"Twentieth Century Psychiatry" (W. W. Norton & Co.).
"Modern Treatment of Nervous and Mental Disease." With Dr. Smith Ely Jelliffe (Lea and Febiger).
"Crimes and Criminals" (Farrar and Rinehart).
"Foundations of Psychiatry" (Nervous and Mental Disease Publishing Company).
"Forty Years of Psychiatry" (Nervous and Mental Disease Publishing Company).
"Medical Psychology" (Nervous and Mental Disease Publishing Company).

It is difficult now and will be increasingly so in the years to come for the medical men of the National Capitol who had come to rely upon Dr. White's wise counsels in trying situations affecting public policy, as well as in matters medical, to realize that he has gone forever from among us.

His wide and constant contacts with men in public life and his long experience in matters before Congress enabled him to render valuable service to local medical organizations as well as to many other such organizations throughout the land. Bills in Congress affecting the healing art were constantly submitted to Dr. White for his opinion, and many were the hidden pitfalls which his keen analytical mind discovered. No day was too crowded for him to pause and respond to the call for aid from a brother practitioner. His friends often marvelled that he could afford the time to attend conferences on civic as well as professional matters. As Superintendent of St. Elizabeths Hospital he was responsible for the well being of approximately six thousand patients and a thousand employees, in addition to the direction of his professional staff. Dr. White would have had little interest in an Institution devoted largely to merely custodial care of the mentally afflicted. The goal set by St. Elizabeths during his Superintendency was curative treatment.

While a student at Cornell he resolved, as Herbert Spencer has asserted, that it is possible for an intelligent man to acquire a comprehensive knowledge of every subject. He recognized the tremendous personal effort that

would be involved in even approximating the accomplishment of this ideal. In setting himself to the task, he determined that while mental medicine should command his prime attention, a wide acquaintance and familiarity with other sciences and with organized effort for political and social advancement would enable him to better serve the cause of his chosen profession.

Thus we find him a voracious reader, not getting books from libraries but purchasing them so that they would always be at hand for ready reference. Astronomy, anthropology, medieval and modern art and architecture, engineering, the principles of the law, sociology, political economy, these are some of the subjects which were read with avidity, and absorbed by his wonderful intellect. Soon it was apparent that important works in foreign tongues must be read in the original. To acquire this facility he enrolled in a foreign language school, mastering German and acquiring a working familiarity with French, Spanish and Italian.

All the while he was devoting himself assiduously to his profession. Recognizing that European Universities and laboratories were forging ahead in the diagnosis and treatment of various forms of mental disorder, he spent several summers as a student at the feet of the masters and in laboratory research. On each return he would apply to the great work at St. Elizabeths important results of his foreign studies and observations.

It was becoming apparent that his understanding of the mental processes of others was made clearer by reason of his general knowledge of other subjects. He must keep abreast of all things touching human life that he might definitely accomplish something for the mentally afflicted.

The field needed many more workers, men and women who would devote themselves intelligently and whole-heartedly to the high purpose for which he was giving his life. These must be thoroughly trained physicians, capable of working with him in the field of mental medicine. Already, with Jelliffe he had written the Outlines of Psychiatry, destined to be a standard textbook in all medical schools of the country. To supplement this and to urge young physicians to enlist in the cause he lectured to students in Washington and New York, wrote an astounding number of books and articles for professional journals, talked before important gatherings throughout the land, and personally developed at St. Elizabeths several score of men and women who attained superintendencies and ranking positions in other hospitals.

Men marveled that he could accomplish so much. The extent of his professional activities seemed boundless. A happy orderliness in all affairs was of material aid in the effectuation of his plans and ambitions. Required by law to live at St. Elizabeths, he made it a practice whenever possible to spend three or four evenings away from the Institution. During these periods he was outside the atmosphere of the abnormal, was circulating among normals, enjoying a change of surroundings, refreshing his mind often at the theatre of which he was a devotee. When so refreshed, he

was ready for more work, and probably the great majority of his books were written between midnight and three in the morning. Then, to use his own confession, he was ready to enjoy the "profundity of sleep."

He introduced military psychiatry in this country, was one of the first Superintendents to place female wards under women physicians, was one of the organizers of the Mental Hygiene movement, attended sessions and took conspicuous part in the activities of many medical societies. The positions and honors that came to him were not regarded as personal, they were concrete evidence that more and more the members of his own profession were recognizing the fact that psychiatry was an important branch of medical science, that the problem of the mind diseased must be kept close to the hearts of all physicians.

There was no spark of professional jealousy in his makeup. He was working for those less fortunately endowed, and all that he acquired was freely given to his associates. He was the recognized leader, but he labored shoulder to shoulder, hand in hand, and in genuine companionship with his co-workers.

When he passed on, it was noticeable that men and women in all walks of life, with no particular personal acquaintance with him but legion in numbers, mourned the loss of one whom they held in personal regard. Why should this be so? Why should persons whom he knew not by name nor by sight feel that they had sustained a loss? The answer lies in the fact that the people long since had been convinced of the sincerity of his desire and purpose to serve his fellow man.

His friend and personal counselor, Frederick A. Fenning of the Washington Bar, has collaborated in the preparation of this paper that expression may be given to some of the underlying motives, to a few of the purely personal aspects of one with whom he enjoyed intimate association for more than thirty-three years.

WILLIAM GERRY MORGAN, M.D., F.A.C.P.,
Secretary General

DR. ELIAS HUDSON BARTLEY

Dr. Elias Hudson Bartley (Fellow), Brooklyn, N. Y., died January 12, 1937, of senility. Dr. Bartley was one of the Founders of the American College of Physicians, and, therefore, had been a Fellow since 1915. He was early elected a member of the Council, now known as the Board of Regents, of the College, and the early Minutes of the organization show that he took a very active part.

Dr. Bartley was born at Bartley, N. J., December 6, 1849, later removing to Princeton, Ill., where he attended the public schools. He received his Bachelor of Science degree from Cornell University in 1873, taught in the Princeton High School for a year and then became Professor of Chemistry at Swarthmore College, Swarthmore, Pa., for three years. He then pur-

sued his medical training at the Long Island College Hospital, graduating in 1879. Immediately thereafter he was appointed Assistant to the Chair of Diseases of Children, Lecturer in Chemistry and Instructor in Chemical Analysis at the Long Island College Hospital. He was promoted to the Professorship of Chemistry and Toxicology in 1886, continuing in that capacity until 1901. Coincident with this, he developed the Department of Pediatrics. He was professor in that department from 1901 to 1915. He was Acting Dean of the Faculty from 1915 to 1917, when he retired as Emeritus Professor of Chemistry and Pediatrics. He was Chief Chemist for the Brooklyn Health Department from 1882 to 1888, a member of the Kings County Board of Pharmacy from 1892 to 1898, and Consulting Pediatrist to the Long Island College Hospital, Methodist Hospital and the Kingston Avenue Hospital, all of Brooklyn, and the Southside Hospital, Bay Shore. For several years he was Chief of the Department of Pediatrics at the Brownsville and East New York Hospital. He was a member of the U. S. Pharmacopeia conventions in 1890, 1900, 1910 and 1930. During his term as Chief Chemist to the Health Department of Brooklyn he organized the first systematic attempt to inspect and control the milk supply of that city. This met with much opposition, but by persistent work and the building up of public sentiment, results began to be obtained. It is said that cholera infantum immediately decreased and finally disappeared. The results he obtained constitute a striking example of public health education backed by the medical profession. In 1902, through the efforts of the Medical Society of the County of Kings, the first Milk Commission was organized, with Dr. Bartley as its chairman. From 1892 to 1902 Dr. Bartley was Dean and Professor of Organic Chemistry at the Brooklyn College of Pharmacy.

The Long Island Medical Journal was founded by Dr. Bartley while he was President of the Associated Physicians of Long Island. In 1912 he was elected President of the Medical Society of the County of Kings. He was a member of the Medical Society of the State of New York, a Fellow of the American Medical Association and a member of its House of Delegates, 1909–10; a member of the New York Academy of Medicine, the Brooklyn Pediatric Society, the Brooklyn Pathological Society and many other organizations. In addition to his Fellowship and Councilorship in the American College of Physicians, he served at one time as a Vice President.

Dr. Bartley was the author of many published articles and of a "Textbook on Medical and Pharmaceutical Chemistry," of which seven editions appeared between 1885 and 1909. He was also the author of a "Manual of Clinical Chemistry," which was published in three succeeding editions.

Although of late years his contacts with the College and his activities have necessarily been diminished, the spirit of his service remains.

DR. JAMES P. McKELVY

Suddenly stricken while en route to Arizona to spend the winter, Dr. James P. McKelvy of Pittsburgh, Pa., died in St. Luke's Hospital, Kansas City, Missouri, on January 28, 1937.

Born in Wilkinsburg, Pa., a suburb of Pittsburgh, December 1, 1869, his preliminary education was obtained at the local public schools and the Pittsburgh High School. After graduation from the latter he studied chemistry at Columbia University and then returned to Pittsburgh to become associated with the manufacturing firm of McIntire-Hemphill Company as chemist.

After three years Dr. McKelvy returned to Columbia University to enter the College of Physicians and Surgeons, from which he graduated in 1901. He served internships for two years at the Roosevelt Hospital and the Sloan Maternity Hospital and then returned to Pittsburgh to take up the practice of medicine.

Dr. McKelvy was attending physician to the Allegheny General Hospital from 1907 to 1925 and Physician-in-Chief from 1925 until his death. He was a member of the Board of Managers of the William H. Singer Memorial Research Laboratory from the time of its establishment in 1916.

President of the Allegheny County Medical Society in 1919, he was also a member of the Pennsylvania State Medical Society, a Fellow of the American Medical Association and the Pittsburgh Academy of Medicine. Elected to Fellowship in the American College of Physicians in June 1917, he was almost a charter member of our organization.

Dr. McKelvy belonged to the Pittsburgh Club; Oakmont Country Club; Allegheny Country Club; Fox Chapel Country Club; University Club and the Seaview Golf Club of Absecon, N. J.

He was a member of the Sixth United Presbyterian Church of Pittsburgh.

Surviving are his son, Mr. William M. McKelvy, a brother and three sisters.

E. Bosworth McCready, M.D., F.A.C.P.,
Governor for Western Pennsylvania

DR. JAMES LESLIE BUSBY

Dr. James Leslie Busby, a Fellow, died in Pasadena on February 18, 1937. Dr. Busby was born in 1890 in Millersport, Ohio. He received his M.D. degree from Ohio State University in 1913, was an intern in St. Clair Hospital, Columbus, in 1913 and 1914 and practiced in Shelby and in Columbus from 1914 to 1918 when he joined the Medical Corps of the Army. He was assistant chief medical advisor in the Bureau of War Risk Insurance and for two years chief of the section of medicine and surgery in the United States Public Health Service. He entered the Mayo Foundation January 1, 1923. He was made an associate in medicine January 1, 1925, and was

an instructor in medicine from 1927 to 1929. He left the Mayo Foundation in August 1929 to practice medicine in Pasadena.

Dr. Busby was a member of the senior staff of the Los Angeles General Hospital and an Associate Professor of Medicine in the College of Medical Evangelists. He was a member of the American Medical Association, the Southern California Medical Association, the Los Angeles Clinical and Pathological Society, the Alumni Association of the Mayo Foundation for Education and Medical Research, and a Fellow of the American College of Physicians. He was on the staff of the Huntington Memorial Hospital and St. Lukes Hospital in Pasadena and chairman of the Medical Advisory Board of the Ruth Home in El Monte, California. Dr. Busby was widely and well known. He enjoyed a large practice and had many professional, civic, and social connections. He will be greatly missed in his community. He is survived by his wife, Louise Busby, and two children.

EGERTON L. CRISPIN, M.D., F.A.C.P.,
Los Angeles, California

DR. DAVID G. GHRIST

Dr. David G. Ghrist, a Fellow of the College, died in the Good Samaritan Hospital in Los Angeles on February 3, 1937, from pneumonia following an attack of influenza.

Dr. Ghrist was born in Ames, Iowa in 1898. He received an A.B. degree from Stanford University in 1921 and an M.D. from Harvard University in 1925. He had an internship in the Los Angeles General Hospital from 1925 to 1926, which was followed by a period of private practice until April 1, 1927, at which time he entered the Mayo Foundation as a Fellow in Medicine. He was appointed a first assistant in his clinical division of medicine April 1, 1929. In 1930 he received a degree of Master of Science from the University of Minnesota.

Dr. Ghrist went from the Mayo Foundation to Los Angeles in October 1930, where he established himself in the practice of internal medicine. His training, ability and personality enabled him to build up a large and satisfactory practice in his chosen field.

Dr. Ghrist was a member of the Beta Theta Pi and Nu Sigma Nu fraternities. He was a member of the Staff of the Good Samaritan Hospital and of St. Vincent's Hospital, and a member of the Association for the Study and Control of Rheumatic Diseases. He was Secretary and Treasurer of the Southern California Medical Association and was Associate Professor of Medicine in the University of Southern California Medical School.

Dr. Ghrist was an able physician whose sterling qualities were admired by all who knew him. He is survived by his widow, Winnefred Ghrist, and by one daughter.

EGERTON L. CRISPIN, M.D., F.A.C.P.,
Los Angeles, California

DR. COLLINS HICKEY JOHNSTON

Dr. Collins H. Johnston (Fellow), died suddenly in his home, Grand Rapids, Michigan, on December 29, 1936. He was seventy-seven years old and was actively engaged in his professional work until the day of his death.

Born in Detroit, Michigan, he graduated from the University of Michigan (Lit.) 1881, (Medicine) 1883, and came to Grand Rapids a few years later. Throughout his busy life he maintained a great interest in the scientific side of medicine. A real student with excellent background, he kept up with the newer things in medicine throughout his long professional life, by means of frequent trips to teaching centers both in this country and abroad. A general practitioner, he had, at different periods, shown very special interest in Pediatrics and Tuberculosis. The special societies to which he belonged attest this interest. He was a member of the American Clinical and Climatological Association, Michigan Trudeau Society, Central States Pediatric Society, and others. At one time he was a member of the House of Delegates of the American Medical Association, and was an ex-president of the Kent County Medical Society. He was on the Visiting Staff of Blodgett Memorial Hospital and Honorary Chief of Staff of D. A. Blodgett Home for Children.

In civic affairs and in his church (Episcopal) he was always an active and willing worker, giving of himself willingly and untiringly. Measures for the promotion of public health always had his interest and for years he campaigned for a pure water supply, and was Chairman of the Medical Milk Commission for safe and good milk. He was largely responsible for the establishment of the Grand Rapids Clinic for Infant Feeding, one of the earliest clinics for this purpose established in the country.

Dr. Johnston will be remembered by his colleagues as an aggressive, industrious and most competent practitioner. His constant, never failing effort to keep abreast of the times, his interest in all things pertaining to medicine, can well serve as a real example to the younger generation.

BURTON R. CORBUS, M.D., F.A.C.P.